SYNOPSIS

NAME OF SPONSOR/COMPANY: Johnson & Johnson Pharmaceutical Research & Development, L.L.C. NAME OF FINISHED PRODUCT: DURAGESIC®/DUROGESIC® NAME OF ACTIVE INGREDIENT(S): Fentanyl	INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER Volume: Page:	(FOR NATIONAL AUTHORITY USE ONLY)

Protocol No.: CR005977

Title of Study: A Study to Assess the Safety, Dose Conversion and Titration of DURAGESIC® (Fentanyl Transdermal System) in Pediatric Subjects With Chronic Pain Requiring Opioid Therapy

Study Initiation/Completion Dates: Start: 24 March 2000; End: 15 December 2004; data cutoff date for interim analysis on 4 February 2002	**Phase of development:** 3

Objectives: Chronic pain / primary objective was to assess the safety of treatment initiation and titration with DURAGESIC® systems of 12.5, 25, 50, 75, and 100 μg/hour in pediatric subjects requiring opioid therapy. A secondary objective was to determine population pharmacokinetics of fentanyl delivered transdermally in a pediatric population. Although not specified as a study objective, evaluations of effectiveness/clinical utility were performed and are included.

Methodology: Single-arm, nonrandomized, open-label, multicenter study with a 15-day primary treatment period followed by a long-term treatment open extension period.

Criteria for Evaluation:

Inclusion Criteria:

- male or female subjects who were at least 2 and <16 years of age;
- suffered chronic pain of a well documented etiology that required continuous administration of opioids. Subject availability for careful monitoring during the first 72 hours following administration of DURAGESIC was also required;
- received opioids continuously for a minimum of 7 days prior to enrollment with a projected need for continuous opioids for at least the length of the primary treatment period (15 days);
- received the equivalent of at least 30 mg of oral morphine the day prior to enrollment based on the dose conversion table provided;
- subject's/child's parent, guardian, or legal representative had signed the informed consent form (ICF); where a child was able to understand the purpose and implications of the trial, his/her assent was also sought;
- a negative serum or urine pregnancy test within 1 week of enrollment for female subjects of child-bearing potential;
- subject/child's parent, guardian comprehended the language of the informed consent (i.e., English, Spanish, Canadian French, etc.), as well as any other communication to the subject/child's parent, guardian given at the investigator site.

Exclusion Criteria:

- skin disease that precluded application of DURAGESIC or which affected the absorption of fentanyl or local tolerability (this did not necessarily exclude lesions which could be avoided);
- use of disallowed concomitant therapy;
- pregnancy or breast feeding;
- known sensitivity to fentanyl, other opioids or adhesives;
- a clinically significant fever (i.e., above 38°C/100.4° F) until the temperature normalizes. Note: Serum fentanyl concentrations could theoretically increase by 30% in subjects with a temperature of 40° C (104°F) due to temperature dependent increases in fentanyl release from the system and increased skin permeability;
- life expectancy of less than the length of the primary treatment period (15 days);
- subjects with pain due to surgery;
- any condition such as clinically significant hepatic or renal dysfunction (3 times the normal values) which, in the judgement of the investigator, may interfere with the adequate safety assessment of DURAGESIC or jeopardize the subjects participation in the study; and
- concomitant treatment with ketoconazole or ritonavir.

SYNOPSIS (CONTINUED)

NAME OF SPONSOR/COMPANY:	INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER	(FOR NATIONAL AUTHORITY USE ONLY)
Johnson & Johnson Pharmaceutical Research & Development, L.L.C. NAME OF FINISHED PRODUCT: DURAGESIC®/DUROGESIC® NAME OF ACTIVE INGREDIENT(S): Fentanyl	Volume: Page:	

Form /dosing route: Transdermal patch applied to nonirradiated skin on a flat surface of the body.

Batch Numbers	12.5 µg/h Patch	25 µg/h Patch	50 µg/h Patch	75 µg/h Patch	100 µg/h Patch
	9801242	195039	9901284	9805175	9805164
	9907880	9910479	9910465	9910457	9910453
		0009249	0013416	0013408	9910878
		0013425	0013418	0016721	0009230
		0016736	0016730	0016725	0013407
					0016717

Dosage: Subjects were converted from oral or parenteral opioids to DURAGESIC on Day 1 by determining total opioid analgesic requirement during the previous 24-hour period. This amount was then converted to the oral morphine-equivalent dose using an Equianalgesic Potency Conversion Table. The starting dose of DURAGESIC was then determined by a conversion table proposed by the sponsor after discussion with the FDA. Following initiation of DURAGESIC treatment, subjects were titrated upwards (no more frequently than every 3 days after the initial dose) until pain was subjectively controlled/improved. Titration steps were based upon supplemental opioid consumption (rescue medication) such that the dose of DURAGESIC was increased by 12.5 µg/hour for every 45 mg of oral morphine equivalents (ME) consumed on the second or third days following the last patch change. The maximum interval increase in patch strength was 25 µg/hour, unless specifically excepted by the sponsor.

Duration of treatment: 15 days for the primary treatment period with continued therapy until DURAGESIC is approved for use in children or until development is stopped.

Duration of trial: 15 days for the primary treatment period with continued therapy until DURAGESIC is approved for use in children or until development is stopped.

Disallowed medication: The use of opioid analgesics was prohibited during the study with the exception of short-acting oral or parenteral opioids to treat breakthrough pain. Fentanyl was prohibited during the study as a rescue medication but could be for surgical purposes if deemed medically appropriate. The concomitant use of ketoconazole or ritonavir was also prohibited. Medications allowed during the study included the short-term use of sufentanil, alfentanil, or remifentanil for conscious sedation (e.g., diagnostic or surgical procedures). Acetaminophen was also allowed for the treatment of headache or fever. The dose of central nervous system (CNS) depressant medications (including benzodiazepines) used during the study was to be reduced by ≥50%. The concomitant use of these medications could result in hypotension.

SYNOPSIS (CONTINUED)

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Statistical Methods

The analyses presented in first report (EDMS-PSDB-2139401:4.0) was based on a closed database consisting of all primary treatment period data from all subjects enrolled in the study and all extension data for subjects who entered the extension treatment period up to a subject's last visit up to and including 4 February 2002. A report of the data from the extension period is provided in the report EDMS-PSDB-4449313: 2.0 from the start of the extension period to the end of the study.

Subject disposition and demographics and baseline characteristics were summarized descriptively. The pharmacokinetic (PK) analysis consisted of listings, descriptive statistical analyses, and graphs of fentanyl serum concentration measures and corresponding dose, time, and demographic data. Observed serum concentration-time data were summarized using descriptive statistics [N, mean, standard deviation (SD), coefficient of variations (CV%), minimum, median, and maximum] by dosage rate. All safety and effectiveness/clinical utility data were summarized for the Intent-to-Treat population (ITT), defined as all enrolled subjects regardless of compliance, unless no DURAGESIC medication was taken. The effectiveness/clinical utility parameters [global assessment, pain levels, play performance, and Child Health Questionnaire (CHQ)] were summarized descriptively by timepoint for the primary treatment period only, overall and by sex and age category. The colored Vertical Visual Analogue Scale (VAS) measure of pain level and CHQ were performed for the age ranges specified by the protocol. The Play Performance Scale (PPS) scores and CHQ were also examined in the context of changes with other clinical utility parameters which included global assessment, pain as reported by the child and parent, average daily dose, and dosing and titration information. Dosing and titration information was summarized descriptively for the primary treatment period, extension period, and both periods combined, overall and by age category, body weight category, and initial DURAGESIC dose. Rescue medications were summarized separately for the primary treatment period and the extension period, overall and by age category, body weight category, and initial DURAGESIC dose.

Adverse event incidence summaries included: overall, by severity, by relationship, those defined to be related to trial medication, serious adverse events, and adverse events leading to withdrawal. All these summaries were presented for all subjects in the ITT population as well as by the subgroups: age category, body weight category, initial DURAGESIC dose, and the Tanner Sexual Maturity Rating Scale. Overall adverse events and adverse events defined to be related to trial medication were also summarized separately for the primary treatment period and extension period, overall and by the same subgroups. Of specific interest was any occurrence of respiratory depression. A listing of subjects with respiratory depression (as reported as an adverse event) was presented and the incidence of this event was acknowledged in each of the above adverse event summaries. Sedation scores were summarized over time. Incidence of bradypnea was also presented. Physical examination results and vital signs were summarized descriptively.

All data obtained and recorded for the primary treatment period and any available extension data for this report are presented in subject data listings for the ITT population, including protocol deviations, deaths, serious adverse events, and adverse events leading to withdrawal.

Safety data for the subjects participating in the extension portion of the study is presented for the events that occurred during the extenison period.

SYNOPSIS (CONTINUED)

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SUMMARY – CONCLUSIONS

Baseline Characteristics – Subject Disposition

A total of 199 subjects were enrolled in the study and included in the ITT population. The majority of subjects (109 subjects, 54.8%) were Caucasian; 43 subjects (21.6%) were Hispanic and 40 subjects (20.1%) were Black. Of 199 subjects, 118 (59.3%) were male and 81 (40.7%) were female. Mean age was 10.7±0.28 years (mean± standard error [SE]). Ninety-four subjects (48.0%) were in the 2-<12 year age group and 102 subjects (52.0%) were in the 12-<16 year age group. Within the 2-<12 age group, 27 subjects (13.8%) were 2-<6 years old and 67 subjects (34.2%) were 6-<12 years old. Three additional subjects had ages that were either <2 years or ≥16 years. All subjects had previously received opioid medication. Of the 79 females and 117 males assessed according to the Tanner Sexual Maturity Rating Scale, 45.6% of females and 53.8% of males were preadolescents (scale range: 1=preadolescent to 5=adult). The initial dose of DURAGESIC for most subjects was 12.5 µg/h (29.6%) or 25.0 µg/h (45.2%). All subjects (100%) received at least 1 previous opioid medication; the most common previous opioid medication was morphine that was taken by 140 subjects (70.4%). The most common concurrent therapies included acetaminophen (paracetamol) (115 subjects, 57.8%), ondansetron (87 subjects, 43.7%), diphenhydramine (85 subjects, 42.7%), ranitidine (71 subjects, 35.7%), red blood cells (70 subjects, 35.2%), potassium (62 subjects, 31.2%), trimethoprim-sulfamethoxazole (Bactrim) (60 subjects, 30.2%), magnesium (54 subjects, 27.1%), and furosemide (51 subjects, 25.6%).

Overall, there were 130 subjects (65.3%) who completed the primary treatment period and entered the extension phase of the study. There were 26 subjects (13.1%) who withdrew during the primary treatment period. Six of these subjects (3%) withdrew due to death and 6 (3%) withdrew due to an adverse event. Insufficient response (3 subjects, 1.5%), ineligibility to continue the trial (3 subjects, 1.5%), withdrawn consent (3 subjects, 1.5%), and noncompliance (2 subjects, 1%) were also given as reasons for discontinuation. The remaining 3 subjects withdrew for other reasons that included “Duragesic no longer needed for pain,” “decreased pain,” and “subject likely discharged.”

Because the duration of treatment in the extension treatment period continued until DURAGESIC was approved for use in children or until development of DURAGESIC was stopped, subjects who entered this period of the study either discontinued treatment or were ongoing. Of the 130 subjects who entered the extension treatment period, 104 subjects (80%) discontinued DURAGESIC treatment during this period prior to the cutoff date. Most of these subjects discontinued trial medication due to death (21 subjects, 16.2%), because they were ineligible to continue the trial (13 subjects, 10%), or because of an adverse event (11 subjects, 8.5%). Withdrawn consent (9 subjects, 6.9%), insufficient response (7 subjects, 5.4%), and noncompliance (1 subjects, 0.8%), were also given as reasons for discontinuing from the study. In addition, 42 of the 104 subjects (32.3%) were included under the category “other” as the reason for discontinuation. Most of these subjects discontinued because pain was improved or resolved, or because subjects were weaned off of opioids (22 subjects). Additional reasons included increased pain (2 subjects) and subject required increased patch changes (2 subjects).

After the cutoff date, 26 subjects continued to be treated.

During the extension period, 130 subjects were treated with DURAGESIC. Of these subjects, most discontinued due to other reasons (47 subjects) death (27 subjects), ineligible to continue (18 subjects), insufficient response (12 subjects), withdrew consent (12 subjects), and adverse events (11 subjects).

SYNOPSIS (CONTINUED)

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Pharmacokinetic Results

Observed serum fentanyl concentrations were by patch, time interval, and dosing rate. Approximately 70% of the evaluable postdose samples were obtained following dosing with 12.5 or 25 µg/hour. A large variability in concentration was observed between subjects, as evidenced by CV generally greater than 50%. Despite the greater variability and limited sample size at higher doses, serum fentanyl concentrations were comparable on average across time intervals following application of the first patch, as well as subsequent patches. When patches were pooled and serum fentanyl concentrations examined across time intervals, a substantial overlap in concentrations across dose levels was observed. This is consistent with observations in an adult population on DURAGESIC patches.

EFFICACY RESULTS:

Effectiveness/clinical utility parameter assessments (global assessment of pain treatment, pain intensity levels assessed by parent/guardian and child, PPS, and dosing and titration information) provide support for using the DURAGESIC patch in subjects aged 2-<16 years with chronic pain requiring the use of a potent opioid. Furthermore, these results suggest that the proposed conversion, titration, and dosing schedules are appropriate.

For subjects who had a global assessment of pain treatment of fair or poor regarding their pain therapy at baseline, 79.4% improved with the DURAGESIC patch to an assessment of good or very good at Day 16 or last visit in the primary treatment period for the DURAGESIC patch. For subjects who had a treatment assessment of good or very good regarding their current pain therapy at baseline, the majority (94.8%) remained so at Day 16 or last visit in the primary treatment period for the DURAGESIC patch. Average daily pain intensity levels decreased steadily over time for both the parent/guardian-reported numeric pain score and the child-reported VAS. Over half of the subjects who completed the primary treatment period (61.3%) never required an upward titration of Duragesic above the initial dose during the primary treatment period. The mean of average daily DURAGESIC dose per kg of body weight was 1.08±0.064 µg/hour/kg and the average initial dose of DURAGESIC per kg of body weight was 0.98±0.057 µg/hour/kg for the ITT population during the primary treatment period. Subjects 2-<6 years of age had the highest per-kilogram dose requirements. The majority of subjects (84.9%) took at least 1 rescue medication, with mean of average oral morphine-equivalent dose per kg of body weight of 1.35±0.163 mg/kg during the primary treatment period. Overall, an improvement in the subject's functioning based on the final PPS scores was observed. Improvements were associated with a reduction of pain intensity as assessed by the child and parent and with the parent's positive assessment of treatment.

SYNOPSIS (CONTINUED)

NAME OF SPONSOR/COMPANY:	INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER	(FOR NATIONAL AUTHORITY USE ONLY)
Johnson & Johnson Pharmaceutical Research & Development, L.L.C. NAME OF FINISHED PRODUCT: DURAGESIC®/DUROGESIC® NAME OF ACTIVE INGREDIENT(S): Fentanyl	Volume: Page:	

SAFETY RESULTS:

Combined Primary and Extension Treatment Periods to cutoff of 4 February 2002	DURAGESIC (ITT Population: N=199)
No. (%) of deaths[a]	53 (26.6)
No. (%) with ≥1 treatment-emergent serious adverse events	86 (43.2)
No. (%) treatment stopped due to adverse events	19 (9.5)
No. (%) with ≥1 treatment-emergent adverse events[b]	180 (90.5)
Most frequent treatment-emergent adverse events (≥10%):	
Fever	71 (35.7)
Vomiting	66 (33.2)
Nausea	42 (21.1)
Headache	37 (18.6)
Abdominal Pain	34 (17.1)
Diarrhea	28 (14.1)
Anemia	26 (13.1)
Pruritus	24 (12.1)
Constipation	23 (11.6)

[a] Includes treatment-emergent and non-treatment-emergent deaths.
[b] For this study, disease progression was an adverse event.

Total Extension Treatment Period	DURAGESIC ITT Population: N=130)
No. (%) of deaths[a]	37 (28.5)
No. (%) with ≥1 treatment-emergent serious adverse events	56 (43.1)
No. (%) treatment stopped due to adverse events[b]	15 (11.5)
No. (%) with ≥1 treatment-emergent adverse events[c]	101 (77.7)
Most frequent treatment-emergent adverse events (≥10%):	
Fever	31 (23.8)
Vomiting	25 (19.2)
Nausea	17 (13.1)
Diarrhea	13 (10.0)
Anemia	23 (17.7)

[a] Includes treatment-emergent deaths that occurred only during the extension treatment period or within 30 days of last treatment of the study for subjects with extension treatment. There were 7 deaths that occurred during the extension treatment period after the cutoff date of 4 February 2002 and 1 death, not included in the 37, that occurred more than 30 days after the last treatment. The total number of deaths for this study including primary and extension treatment was 61.
[b] Three subjects discontinued treatment after the cutoff date of 4 February 2002.
[c] For this study, disease progression was an adverse event.

SYNOPSIS (CONTINUED)

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SAFETY RESULTS (CONTINUED):

In subjects who were treated during the primary period and the extension period up to the cutoff date of 4 February 2002, DURAGESIC (fentanyl) was found to be safe and well tolerated in this population of male and female pediatric subjects (2 to <16 years of age) with chronic pain. Age, body weight category, initial DURAGESIC dose by body weight, and sexual maturity (prepubertal versus pubertal) had no apparent clinically relevant effects on the overall safety profile of DURAGESIC. Fifty-three subjects (26.6%) died during the study up to the cutoff date of 4 February 2002. Except for 1 adverse event of neuroblastoma that was considered by the investigator to have a "doubtful" relationship to trial medication, none of the other 52 deaths were considered by the investigator to be related to treatment with DURAGESIC. As expected in this target subject population, deaths, adverse events, and serious adverse events were primarily associated with the subject's underlying disease.

The overall incidence of serious adverse events during the combined primary and extension treatment periods in subjects before the cutoff date was 43.2% (86 subjects), and the most common serious adverse event was fever (21 subjects, 10.6%). The incidence of serious adverse events was similar during the primary treatment period (30.2%) and during the extension treatment period (31.5%). Nineteen subjects (9.5%) had serious adverse events that were considered related to treatment with DURAGESIC. The most common serious adverse events related to trial medication were vomiting (2.5%) and pain (2%). The serious adverse event profile was typical of a pediatric oncology population and none of the reported serious adverse events indicate a specific risk in this subject population.

Nineteen subjects prior to the cutoff date (9.5%) had an adverse event that lead to discontinuation from the study; 7 subjects withdrew during the primary treatment period and 12 subjects withdrew during the extension treatment period. Nausea, vomiting, stupor, and fever, each reported by 2 subjects, were the most common adverse events leading to withdrawal from the study. The majority of subjects who had an adverse event that led to discontinuation were in the 12-<16 years age group (14 subjects). Ten of the 19 subjects withdrew due to adverse events that were considered related to trial medication; four subjects each were receiving DURAGESIC at a dose of 12.5 μg/h (0.19 to 1.79 μg/h/kg) or 25.0 μg/h (0.52 to 1.19 μg/h/kg) at the time of onset of the adverse events that led to withdrawal.

Eighteen subjects had at least 1 adverse event that resulted in a dose adjustment of their trial medication; 11 subjects had increases, 6 subjects had decreases, and 1 subject had both an increase and decrease in response to different adverse events. Nine of the 11 subjects who had increased dose adjustments involved adverse events related to pain.

Five subjects had their dose of DURAGESIC decreased due to 6 adverse events that were considered either possibly (dyskinesia and nausea), probably (somnolence), or very likely (pruritus) related to trial medication. Two other subjects had their dose of Duragesic decreased due to medication errors (incorrect dose of DURAGESIC and possible benzodiazepine overdose).

Most subjects (90.5%) reported at least 1 adverse event during treatment prior to the cutoff date. The incidence of adverse events was higher during the primary treatment period (86.4%) compared with the extension treatment period (66.2%). The most frequent adverse events during treatment were fever (35.7%), vomiting (33.2%), nausea (21.1%), headache (18.6%), abdominal pain (17.1%), diarrhea (14.1%), anemia (13.1%), pruritus (12.1%), and constipation (11.6%). This profile is consistent with clinical experience in this subject population of largely pediatric oncology subjects on multiple concomitant medications, including chemotherapeutic agents.

SYNOPSIS (CONTINUED)

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SAFETY RESULTS (CONTINUED):

About one-half of the subjects (50.3%) before the cutoff date had at least 1 adverse event that was considered by the investigator to be related to trial medication. The most common adverse events related to treatment with DURAGESIC were vomiting (16.1%), nausea (10.6%), pruritus (7.5%), application site reaction (7.5%), headache (7.0%), constipation (6.0%), and somnolence (5.5%). This pattern of adverse events is similar to that observed in adult subjects and is the expected profile of an opioid analgesic. Analysis of adverse events commonly associated with opioid use in subjects before the cutoff date, including gastrointestinal symptoms and respiratory depression, raised no unexpected safety concerns. In particular, the incidence of vomiting, nausea, and constipation considered very likely, probably, or possibly related to trial medication was low during the primary (≤6%) and extension (<4%) treatment periods. All reports of these adverse events considered serious were either not related or of doubtful relationship to treatment with Duragesic. Further, only one subject during the primary and one subject during the extension treatment period discontinued from the study due to gastrointestinal symptoms considered possibly related to treatment.

Most adverse events, that occurred during treatment in subjects before the cutoff date were suggestive of respiratory depression and were not related to treatment with DURAGESIC. Three subjects had events that were considered probably (respiratory depression) or possibly (bradypnea, bronchospasm) related to trial medication. One subject experienced respiratory disorder (increased tachypnea) that was of doubtful relationship to treatment. In addition, during the 72-hour application period of the first DURAGESIC patch, there were no subjects who showed a frequency or pattern of decreased respiration that was of concern or required medical intervention. Also, during this application period mean daily sedation scores decreased over time but they remained above scores corresponding to a state of moderate alertness.

Although there were some reports of application site reactions associated with the use of the DURAGESIC patch during treatment in subjects before the cutoff date, the incidence was low (8.5%) and no subject had an application site reaction that was considered serious. There was only one event (redness at patch site) considered very likely related to treatment that resulted in withdrawal from the study.

Mean daily sedation scores in subjects before the cutoff date, (assessed every 4 hours during the first 72 hours following application of the first DURAGESIC patch) decreased over time (Day 1: 2.65; Day 2: 2.27; and endpoint: 2.13) but remained above scores that indicate a state of moderate alertness (sedation score=2). In addition, no subject experienced bradypnea during the first 72 hours of treatment with DURAGESIC.

Evaluation of vital signs and physical examination data did not disclose any safety concerns in subjects before the cutoff date.

There were no new safety findings in 26 subjects who continued with extension treatment after the cutoff date of 4 February 2002. There were an additional 7 deaths and 3 discontinuations associated with adverse events in these 26 subjects. One death occurred greater than 30 days after the last treatment.

SYNOPSIS (CONTINUED)

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CONCLUSION:

The primary objective of this trial was to identify the safety profile of DURAGESIC in the intended target population (children and adolescents aged 2 to 16 years). Safety is relevant only when determined at clinically meaningful doses, which in the case of opioids is dependent upon each individual subject's need. As such, integral to the determination of safety is validation of a conversion table for initiation of therapy and appropriate guidance for titrating to effective dose. The proposed conversion table and titration algorithm used in this trial appear to be valid, with approximately 60% of subjects not requiring upward titration during the primary treatment period. Of those requiring titration, most were able to achieve adequate analgesia within two dose cycles (less than 6 days). DURAGESIC provided >80% of daily opioid requirement during the primary treatment period, with a clear decrease in rescue medication requirement over the 15-day treatment period. Pain relief improves over the treatment period, as does overall satisfaction (subject and/or parent). Additional measures of clinical effectiveness such as the Play-Performance Scale and the Child Health Questionnaire also indicate positive response to DURAGESIC therapy.

Having confirmed that the proposed dosing regimen is therapeutically appropriate, the safety profile determined in this trial can be considered as a valid index of the target population. The observed adverse events are consistent with that of a potent opioid in a population with serious medical conditions. There are no adverse events associated with DURAGESIC that indicate a pediatric-specific risk. Using a list of opioid-related effects as a marker, the assessment that the initial dose conversion is appropriate (providing neither too much or too little opioid) is confirmed.

Analysis by age and other subgroups discloses no apparent differences in response characteristics or safety profile relative to DURAGESIC. The younger age group, by virtue of lower body weight relative to the minimum available dose of DURAGESIC, entered the study with a higher opioid dose per kilogram than the older children and adolescents. This unavoidable selection bias is reflected in the general severity of disease states in the youngest age group. Adverse events that occur with greater frequency in the younger age group (fever, anemia) appear to be related to systemic disease or concomitant medical therapies rather than to DURAGESIC.

Overall, DURAGESIC is a safe and effective alternative to oral opioid therapy in children requiring at least 30 mg of oral ME per day. The proposed conversion table and titration algorithm are appropriate in this population, as is the suggested dosing interval. There is no risk in the pediatric population beyond that expected with the use of opioids for the relief of pain associated with serious illness and there does not appear to be any pediatric-specific risk associated with DURAGESIC in children as young as two years old.

Serum concentrations of fentanyl showed considerable intersubject variability, however the variability observed in this study was comparable to the variability observed in the adult population on DURAGESIC patches. Exposure to fentanyl generally increased with dose, but substantial overlap existed across doses, as previously seen in adult subjects. It was not possible to observe clear dose proportionality in this study due to sparse data, however, fentanyl serum concentrations, normalized to 12.5 ug/hr were similar indicating a possible correlation between dose and exposure.

Date of the report: 1 September 2005

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