CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

19-813 / S-036

Trade Name: **Duragesic**

Generic Name: **Fentanyl Transdermal System**

Sponsor: **Alza Corporation**

Approval Date: **May 20, 2003**

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APPLICATION NUMBER:

19-813 / S-036

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APPLICATION NUMBER:

19-813 / S-036

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 19-813/S-036

Alza Corporation
1900 Charleston Road
Mountain View, CA 94043

Attention: Janne Wissel
Senior Vice President, Operations

Dear Ms. Wissel:

Please refer to your supplemental new drug application dated November 25, 2002, received November 26, 2002, submitted under section 505(b)/pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Duragesic® (Fentanyl Transdermal System).

We acknowledge receipt of your submissions dated January 7 and 14, March 25, and May 12, 2003.

This supplemental new drug application provides for use of Duragesic® (Fentanyl Transdermal System) in pediatric patients 2 years of age and older.

We have completed our review of this application, as amended, and it is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

The final printed labeling (FPL) must be identical to the enclosed labeling text for the package insert and the patient package insert.

Please submit the FPL electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format – NDA. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved supplement NDA 19-813/S-036." Approval of this submission by FDA is not required before the labeling is used.

FDA's Pediatric Rule [at 21 CFR 314.55/21 CFR 601.27] was challenged in court. On October 17, 2002, the court ruled that FDA did not have the authority to issue the Pediatric Rule and has barred FDA from enforcing it. Although the government decided not to pursue an appeal in the courts, it will work with Congress in an effort to enact legislation requiring pharmaceutical manufacturers to conduct appropriate pediatric clinical trials. In addition, third party interveners have decided to appeal the court's decision striking down the rule. Therefore, we encourage you to submit a pediatric plan that describes development of your product in the pediatric population where it may be used. Please be aware that whether or not this pediatric plan and subsequent submission of pediatric data will be required depends upon passage of legislation or the success of the third party appeal. In any event, we

hope you will decide to submit a pediatric plan and conduct the appropriate pediatric studies to provide important information on the safe and effective use of this drug in the relevant pediatric populations.

The pediatric exclusivity provisions of FDAMA as reauthorized by the Best Pharmaceuticals for Children Act are not affected by the court's ruling. Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products. You should refer to the Guidance for Industry on Qualifying for Pediatric Exclusivity (available on our web site at www.fda.gov/cder/pediatric) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request". FDA generally does not consider studies submitted to an NDA before issuance of a Written Request as responsive to the Written Request. Applicants should obtain a Written Request before submitting pediatric studies to an NDA.

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to this division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

Please submit one market package of the drug product when it is available.

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Kimberly Compton, Regulatory Project Manager, at (301) 827-7432.

Sincerely,

{See appended electronic signature page}

Bob Rappaport, M.D.
Acting Director
Division of Anesthetic, Critical Care, and
Addiction Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosures

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Bob Rappaport
5/20/03 06:12:09 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-813 / S-036

LABELING

DURAGESIC®
(FENTANYL TRANSDERMAL SYSTEM) CII

Full Prescribing Information

BECAUSE SERIOUS OR LIFE-THREATENING HYPOVENTILATION COULD OCCUR, DURAGESIC® (FENTANYL TRANSDERMAL SYSTEM) IS CONTRAINDICATED:

- In the management of acute or post-operative pain, including use in out-patient surgeries
- **In the management of mild or intermittent pain responsive to PRN or non-opioid therapy**
- **In doses exceeding 25 µg/h at the initiation of opioid therapy**

(See CONTRAINDICATIONS for further information.)

SAFETY OF DURAGESIC® HAS NOT BEEN ESTABLISHED IN CHILDREN UNDER 2 YEARS OF AGE. DURAGESIC® SHOULD BE ADMINISTERED TO CHILDREN ONLY IF THEY ARE OPIOID-TOLERANT AND AGE 2 YEARS OR OLDER (See PRECAUTIONS - Pediatric Use.)

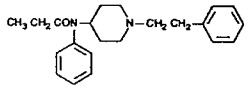
DURAGESIC® is indicated for treatment of chronic pain (such as that of malignancy) that:

- **Cannot be managed by lesser means such as acetaminophen-opioid combinations, non-steroidal analgesics, or PRN dosing with short-acting opioids and**
- **Requires continuous opioid administration.**

The 50, 75, and 100 µg/h dosages should ONLY be used in patients who are already on and are tolerant to opioid therapy.

DESCRIPTION

DURAGESIC® (fentanyl transdermal system) is a transdermal system providing continuous systemic delivery of fentanyl, a potent opioid analgesic, for 72 hours. The chemical name is N-Phenyl-N-(1-2-phenylethyl-4-piperidyl) propanamide. The structural formula is:



The molecular weight of fentanyl base is 336.5, and the empirical formula is $C_{22}H_{28}N_2O$. The n-octanol:water partition coefficient is 860:1. The pKa is 8.4.

System Components and Structure

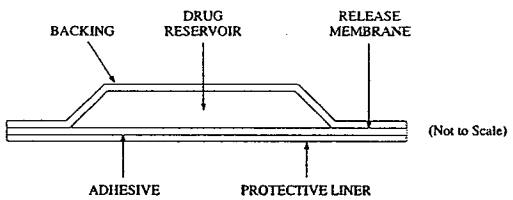
The amount of fentanyl released from each system per hour is proportional to the surface area (25 µg/h per 10 cm^2). The composition per unit area of all system sizes is identical. Each system also contains 0.1 mL of alcohol USP per 10 cm^2.

Dose* (µg/h)	Size (cm^2)	Fentanyl Content (mg)
25	10	2.5
50**	20	5
75**	30	7.5
100**	40	10

*Nominal delivery rate per hour
**FOR USE ONLY IN OPIOID TOLERANT PATIENTS

DURAGESIC® is a rectangular transparent unit comprising a protective liner and four functional layers. Proceeding from the outer surface toward the surface adhering to skin, these layers are:

1) A BACKING LAYER OF POLYESTER FILM; 2) A DRUG RESERVOIR OF FENTANYL AND ALCOHOL USP GELLED WITH HYDROXYETHYL CELLULOSE; 3) AN ETHYLENE-VINYL ACETATE COPOLYMER MEMBRANE THAT CONTROLS THE RATE OF FENTANYL DELIVERY TO THE SKIN SURFACE; AND 4) A FENTANYL CONTAINING SILICONE ADHESIVE. BEFORE USE, A PROTECTIVE LINER COVERING THE ADHESIVE LAYER IS REMOVED AND DISCARDED.



The active component of the system is fentanyl. The remaining components are pharmacologically inactive. Less than 0.2 mL of alcohol is also released from the system during use.

Do not cut or damage DURAGESIC®. If the DURAGESIC® system is cut or damaged, controlled drug delivery will not be possible.

CLINICAL PHARMACOLOGY

Pharmacology

Fentanyl is an opioid analgesic. Fentanyl interacts predominantly with the opioid µ-receptor. These µ-binding sites are discretely distributed in the human brain, spinal cord, and other tissues.

In clinical settings, fentanyl exerts its principal pharmacologic effects on the central nervous system. Its primary actions of therapeutic value are analgesia and sedation. Fentanyl may increase the patient's tolerance for pain and decrease the perception of suffering, although the presence of the pain itself may still be recognized.

In addition to analgesia, alterations in mood, euphoria and dysphoria, and drowsiness commonly occur. Fentanyl depresses the respiratory centers, depresses the cough reflex, and constricts the pupils. Analgesic blood levels of fentanyl may cause nausea and vomiting directly by stimulating the chemoreceptor trigger zone, but nausea and vomiting are significantly more common in ambulatory than in recumbent patients, as is postural syncope.

OPIOIDS INCREASE THE TONE AND DECREASE THE PROPULSIVE CONTRACTIONS OF THE SMOOTH MUSCLE OF THE GASTROINTESTINAL TRACT. THE RESULTANT PROLONGATION IN GASTROINTESTINAL TRANSIT TIME MAY BE RESPONSIBLE FOR THE CONSTIPATING EFFECT OF FENTANYL. BECAUSE OPIOIDS MAY INCREASE BILIARY TRACT PRESSURE, SOME PATIENTS WITH BILIARY COLIC MAY EXPERIENCE WORSENING RATHER THAN RELIEF OF PAIN.

While opioids generally increase the tone of urinary tract smooth muscle, the net effect tends to be variable, in some cases producing urinary urgency, in others, difficulty in urination.

At therapeutic dosages, fentanyl usually does not exert major effects on the cardiovascular system. However, some patients may exhibit orthostatic hypotension and fainting.

Histamine assays and skin wheal testing in man indicate that clinically significant histamine release rarely occurs with fentanyl administration. Assays in man show no clinically significant histamine release in dosages up to 50 μg/kg.

Pharmacokinetics (see graph and tables)
DURAGESIC® (fentanyl transdermal system) releases fentanyl from the reservoir at a nearly constant amount per unit time. The concentration gradient existing between the saturated solution of drug in the reservoir and the lower concentration in the skin drives drug release. Fentanyl moves in the direction of the lower concentration at a rate determined by the copolymer release membrane and the diffusion of fentanyl through the skin layers. While the actual rate of fentanyl delivery to the skin varies over the 72 hour application period, each system is labeled with a nominal flux which represents the average amount of drug delivered to the systemic circulation per hour across average skin.

While there is variation in dose delivered among patients, the nominal flux of the systems (25, 50, 75, and 100 μg of fentanyl per hour) is sufficiently accurate as to allow individual titration of dosage for a given patient. The small amount of alcohol which has been incorporated into the system enhances the rate of drug flux through the rate-limiting copolymer membrane and increases the permeability of the skin to fentanyl.

Following DURAGESIC® application, the skin under the system absorbs fentanyl, and a depot of fentanyl concentrates in the upper skin layers. Fentanyl then becomes available to the systemic circulation. Serum fentanyl concentrations increase gradually following initial DURAGESIC® application, generally leveling off between 12 and 24 hours and remaining relatively constant, with some fluctuation, for the remainder of the 72 hour application period. Peak serum concentrations of fentanyl generally occurred between 24 and 72 hours after initial application (see Table A). Serum fentanyl concentrations achieved are proportional to the DURAGESIC® delivery rate. With continuous use, serum fentanyl concentrations continue to rise for the first few system applications. After several sequential 72-hour applications, patients reach and maintain a steady state serum concentration that is

determined by individual variation in skin permeability and body clearance of fentanyl (see graph and Table B).

After system removal, serum fentanyl concentrations decline gradually, falling about 50% in approximately 17 (range 13-22) hours. Continued absorption of fentanyl from the skin accounts for a slower disappearance of the drug from the serum than is seen after an IV infusion, where the apparent half-life is approximately 7 (range 3-12) hours.

Serum Fentanyl Concentrations
Following Multiple Applications of DURAGESIC® 100 µg/h (n=10)

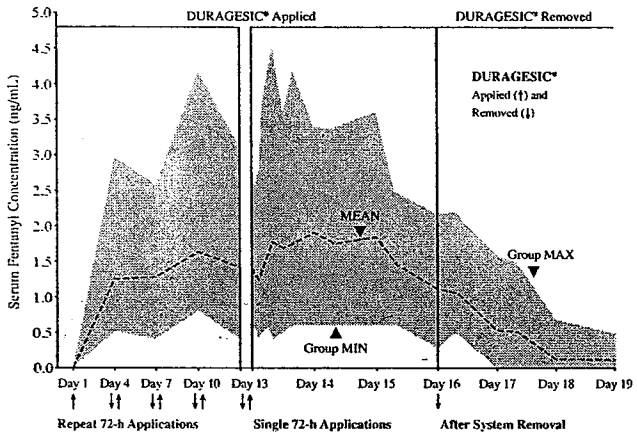


TABLE A
FENTANYL PHARMACOKINETIC PARAMETERS
FOLLOWING FIRST 72-HOUR APPLICATION OF DURAGESIC®

Dose	Mean (SD) Time to Maximal Concentration T_{max} (h)	Mean (SD) Maximal Concentration C_{max} (ng/mL)
DURAGESIC® 25 µg/h	38.1 (18.0)	0.6 (0.3)
DURAGESIC® 50 µg/h	34.8 (15.4)	1.4 (0.5)
DURAGESIC® 75 µg/h	33.5 (14.5)	1.7 (0.7)
DURAGESIC® 100 µg/h	36.8 (15.7)	2.5 (1.2)

NOTE: After system removal there is continued systemic absorption from residual fentanyl in the skin so that serum concentrations fall 50%, on average, in 17 hours

TABLE B
. RANGE OF PHARMACOKINETIC PARAMETERS
OF INTRAVENOUS FENTANYL IN PATIENTS

	Clearance (L/h) Range [70 kg]	Volume of Distribution V_{SS} (L/kg) Range	Half-Life $t_{1/2}$ (h) Range
Surgical Patients	27 - 75	3 – 8	3 - 12
Hepatically Impaired Patients	3 - 80^{+}	0.8 – 8^{+}	4 - 12^{+}
Renally Impaired Patients	30 - 78	–	–

$^{+}$Estimated

NOTE: Information on volume of distribution and half-life not available for renally impaired patients.

Fentanyl plasma protein binding capacity decreases with increasing ionization of the drug. Alterations in pH may affect its distribution between plasma and the central nervous system. Fentanyl accumulates in the skeletal muscle and fat and is released slowly into the blood. The average volume of distribution for fentanyl is 6 L/kg (range 3-8; N=8).

In 1.5 - 5 year old non-opioid-tolerant pediatric patients, the fentanyl plasma levels were approximately twice as high as that of the adult patients. In older pediatric age patients the pharmacokinetic parameters were similar to that of the adults. However, these findings have been taken into consideration in determining the dosing recommendations for pediatric patients. For pediatric dosing information, refer to DOSAGE and ADMINISTRATION section.

The kinetics of fentanyl in geriatric patients has not been well studied, but in geriatric patients the clearance of IV fentanyl may be reduced and the terminal half-life greatly prolonged (see PRECAUTIONS).

Fentanyl is metabolized primarily via human cytochrome P450 3A4 isoenzyme system. In humans the drug appears to be metabolized primarily by oxidative N-dealkylation to norfentanyl and other inactive metabolites that do not contribute materially to the observed activity of the drug. Within 72 hours of IV fentanyl administration, approximately 75% of the dose is excreted in urine, mostly as metabolites with less than 10% representing unchanged drug. Approximately 9% of the dose is recovered in the feces, primarily as metabolites. Mean values for unbound fractions of fentanyl in plasma are estimated to be between 13 and 21%.

Skin does not appear to metabolize fentanyl delivered transdermally. This was determined in a human keratinocyte cell assay and in clinical studies in which 92% of the dose delivered from the system was accounted for as unchanged fentanyl that appeared in the systemic circulation.

Pharmacodynamics

Analgesia

DURAGESIC® is a strong opioid analgesic. In controlled clinical trials in non-opioid-tolerant patients, 60 mg/day IM morphine was considered to provide analgesia approximately equivalent to DURAGESIC® 100 μg/h in an acute pain model.

Minimum effective analgesic serum concentrations of fentanyl in opioid naive adult patients range from 0.2 to 1.2 ng/mL; side effects increase in frequency at serum levels above 2 ng/mL. Both the minimum effective concentration and the concentration at which toxicity occurs rise with increasing tolerance. The rate of development of tolerance varies widely among individuals.

Ventilatory Effects

At equivalent analgesic serum concentrations, fentanyl and morphine produce a similar degree of hypoventilation. A small number of patients have experienced clinically significant hypoventilation with DURAGESIC®. Hypoventilation was manifested by respiratory rates of less than 8 breaths/minute or a pCO_2 greater than 55 mm Hg. In clinical trials of 357 postoperative (acute pain) patients treated with DURAGESIC®, 13 patients experienced hypoventilation. In these studies the incidence of hypoventilation was higher in nontolerant women (10) than in men (3) and in patients weighing less than 63 kg (9 of 13). Although patients with impaired respiration were not common in the trials, they had higher rates of hypoventilation. In addition, post-marketing reports have been received of opioid-naive post-operative patients who have experienced clinically significant hypoventilation with DURAGESIC®. DURAGESIC® is contraindicated in the treatment of postoperative and acute pain.

While most adult and pediatric patients using DURAGESIC® chronically develop tolerance to fentanyl induced hypoventilation, episodes of slowed respirations may occur at any time during therapy; medical intervention generally was not required in these instances.

Hypoventilation can occur throughout the therapeutic range of fentanyl serum concentrations. However, in non-opioid-tolerant patients the risk of hypoventilation increases at serum fentanyl concentrations greater than 2 ng/mL, especially for patients who have an underlying pulmonary condition or who receive usual doses of opioids or other CNS drugs associated with hypoventilation in addition to DURAGESIC®. The use of initial doses in adults exceeding 25 µg/h is contraindicated in patients who are not tolerant to opioid therapy. DURAGESIC® should be administered to children only if they are opioid-tolerant and age 2 years or older.

The use of DURAGESIC® should be monitored by clinical evaluation. As with other drug level measurements, serum fentanyl concentrations may be useful clinically, although they do not reflect patient sensitivity to fentanyl and should not be used by physicians as a sole indicator of effectiveness or toxicity.

See BOX WARNING, CONTRAINDICATIONS, WARNINGS, PRECAUTIONS, ADVERSE REACTIONS and OVERDOSAGE for additional information on hypoventilation.

Cardiovascular Effects

Fentanyl may infrequently produce bradycardia. The incidence of bradycardia in clinical trials with DURAGESIC® was less than 1%.

CNS Effects

IN OPIOID NAIVE PATIENTS, CENTRAL NERVOUS SYSTEM EFFECTS INCREASE WHEN SERUM FENTANYL CONCENTRATIONS ARE GREATER THAN 3 NG/ML.

CLINICAL TRIALS

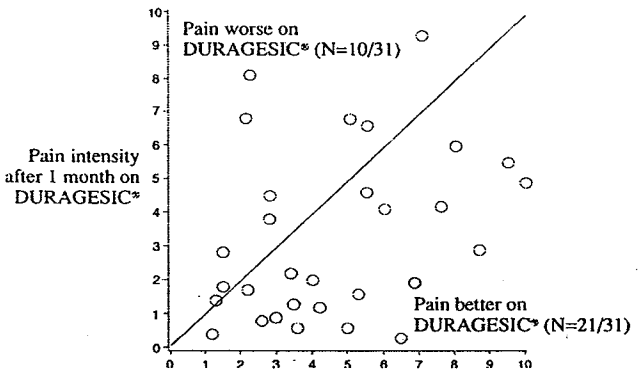
Adults

DURAGESIC® (fentanyl transdermal system) was studied in patients with acute and chronic pain (postoperative and cancer pain models); however, DURAGESIC® is contraindicated for postoperative analgesia.

The analgesic efficacy of DURAGESIC® was demonstrated in an acute pain model with surgical procedures expected to produce various intensities of pain (eg, hysterectomy, major orthopedic surgery). Clinical use and safety was evaluated in patients experiencing chronic pain due to malignancy. Based on the results of these trials, DURAGESIC® was determined to be effective in both populations, but safe only for use in patients with chronic pain. Because of the risk of hypoventilation (4% incidence) in postoperative patients with acute pain, DURAGESIC® is contraindicated for postoperative analgesia. (See BOX WARNING, CLINICAL PHARMACOLOGY-Ventilatory Effects, and CONTRAINDICATIONS.)

DURAGESIC® as therapy for pain due to cancer has been studied in 153 patients. In this patient population, DURAGESIC® has been administered in doses of 25 µg/h to 600 µg/h. Individual patients have used DURAGESIC® continuously for up to 866 days. At one month after initiation of DURAGESIC® therapy, patients generally reported lower pain intensity scores as compared to a prestudy analgesic regimen of oral morphine (see graph).

Visual Analogue Score of Pain Intensity Ratings at Entry in the Study and After One Month of DURAGESIC® Use



Pain Intensity on Pre-Study Analgesic Regimen

Pediatrics
The safety of DURAGESIC® was evaluated in three open-label trials in 291 pediatric patients, 2 years through 18 years of age, with chronic pain. Starting doses of 25µg/h and higher were used by 181 patients. Approximately 90% of the total daily opioid requirement (DURAGESIC® plus rescue medication) was provided by DURAGESIC®.

INDICATIONS AND USAGE

DURAGESIC® (fentanyl transdermal system) is indicated in the management of chronic pain in patients who require continuous opioid analgesia for pain that cannot be managed by lesser means such as acetaminophen-opioid combinations, non-steroidal analgesics, or PRN dosing with short-acting opioids.

DURAGESIC® should not be used in the management of acute or postoperative pain because serious or life-threatening hypoventilation could result. (See BOX WARNING and CONTRAINDICATIONS.)

In patients with chronic pain, it is possible to individually titrate the dose of the transdermal system to minimize the risk of adverse effects while providing analgesia. In properly selected patients, DURAGESIC® is a safe and effective alternative to other opioid regimens. (See DOSAGE AND ADMINISTRATION.)

CONTRAINDICATIONS

BECAUSE SERIOUS OR LIFE-THREATENING HYPOVENTILATION COULD OCCUR, DURAGESIC® (FENTANYL TRANSDERMAL SYSTEM) IS CONTRAINDICATED:

- **In the management of acute or post-operative pain, including use in out-patient surgeries because there is no opportunity for proper dose titration (See CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION),**
- **In the management of mild or intermittent pain that can otherwise be managed by lesser means such as acetaminophen-opioid combinations, non-steroidal analgesics, or PRN dosing with short-acting opioids, and**
- **In doses exceeding 25 µg/h at the initiation of opioid therapy because of the need to individualize dosing by titrating to the desired analgesic effect.**

DURAGESIC® is also contraindicated in patients with known hypersensitivity to fentanyl or adhesives.

WARNINGS

The safety of DURAGESIC has not been established in children under 2 years of age. DURAGESIC® SHOULD BE ADMINISTERED TO CHILDREN ONLY IF THEY ARE OPIOID-TOLERANT AND AGE 2 YEARS OR OLDER **(See PRECAUTIONS-Pediatric Use.)**

PATIENTS WHO HAVE EXPERIENCED ADVERSE EVENTS SHOULD BE MONITORED FOR AT LEAST 12 HOURS AFTER DURAGESIC® REMOVAL SINCE SERUM FENTANYL CONCENTRATIONS DECLINE GRADUALLY AND REACH AN APPROXIMATE 50% REDUCTION IN SERUM CONCENTRATIONS 17 HOURS AFTER SYSTEM REMOVAL.

DURAGESIC® SHOULD BE PRESCRIBED ONLY BY PERSONS KNOWLEDGEABLE IN THE CONTINUOUS ADMINISTRATION OF POTENT OPIOIDS, IN THE MANAGEMENT OF PATIENTS RECEIVING POTENT OPIOIDS FOR TREATMENT OF PAIN, AND IN THE

DETECTION AND MANAGEMENT OF HYPOVENTILATION INCLUDING THE USE OF OPIOID ANTAGONISTS.
THE CONCOMITANT USE OF OTHER CENTRAL NERVOUS SYSTEM DEPRESSANTS, INCLUDING OTHER OPIOIDS, SEDATIVES OR HYPNOTICS, GENERAL ANESTHETICS, PHENOTHIAZINES, TRANQUILIZERS, SKELETAL MUSCLE RELAXANTS, SEDATING ANTIHISTAMINES, AND ALCOHOLIC BEVERAGES MAY PRODUCE ADDITIVE DEPRESSANT EFFECTS. HYPOVENTILATION, HYPOTENSION AND PROFOUND SEDATION OR COMA MAY OCCUR. WHEN SUCH COMBINED THERAPY IS CONTEMPLATED, THE DOSE OF ONE OR BOTH AGENTS SHOULD BE REDUCED BY AT LEAST 50%.

ALL PATIENTS AND THEIR CAREGIVERS SHOULD BE ADVISED TO AVOID EXPOSING THE DURAGESIC® APPLICATION SITE TO DIRECT EXTERNAL HEAT SOURCES, SUCH AS HEATING PADS OR ELECTRIC BLANKETS, HEAT LAMPS, SAUNAS, HOT TUBS, AND HEATED WATER BEDS, ETC., WHILE WEARING THE SYSTEM. THERE IS A POTENTIAL FOR TEMPERATURE-DEPENDENT INCREASES IN FENTANYL RELEASE FROM THE SYSTEM. (See PRECAUTIONS - Patients with Fever/External Heat.)

PRECAUTIONS

General

DURAGESIC® (fentanyl transdermal system) doses greater than 25 µg/h are too high for initiation of therapy in non-opioid-tolerant patients and should not be used to begin DURAGESIC® therapy in these patients. Children converting to DURAGESIC® should be opioid-tolerant (See BOX WARNING). DURAGESIC® may impair mental and/or physical ability required for the performance of potentially hazardous tasks (eg, driving, operating machinery). Patients who have been given DURAGESIC® should not drive or operate dangerous machinery unless they are tolerant to the side effects of the drug.

Patients and their caregivers should be instructed to keep both used and unused systems out of the reach of children. Used systems should be folded so that the adhesive side of the system adheres to itself and flushed down the toilet immediately upon removal. Patients should be advised to dispose of any systems remaining from a prescription as soon as they are no longer needed. Unused systems should be removed from their pouch and flushed down the toilet.

Hypoventilation (Respiratory Depression)

Hypoventilation may occur at any time during the use of DURAGESIC®.
Because significant amounts of fentanyl are absorbed from the skin for 17 hours or more after the system is removed, hypoventilation may persist beyond the removal of DURAGESIC®. Consequently, patients with hypoventilation should be carefully observed for degree of sedation and their respiratory rate monitored until respiration has stabilized.

The use of concomitant CNS active drugs requires special patient care and observation. (See WARNINGS.)

Chronic Pulmonary Disease

Because potent opioids can cause hypoventilation, DURAGESIC® (fentanyl transdermal system) should be administered with caution to patients with pre-existing medical conditions predisposing them

to hypoventilation. In such patients, normal analgesic doses of opioids may further decrease respiratory drive to the point of respiratory failure.

Head Injuries and Increased Intracranial Pressure

DURAGESIC® should not be used in patients who may be particularly susceptible to the intracranial effects of CO_2 retention such as those with evidence of increased intracranial pressure, impaired consciousness, or coma. Opioids may obscure the clinical course of patients with head injury. DURAGESIC® should be used with caution in patients with brain tumors.

Cardiac Disease

FENTANYL MAY PRODUCE BRADYCARDIA. FENTANYL SHOULD BE ADMINISTERED WITH CAUTION TO PATIENTS WITH BRADYARRHYTHMIAS.

Hepatic or Renal Disease

At the present time insufficient information exists to make recommendations regarding the use of DURAGESIC® in patients with impaired renal or hepatic function. If the drug is used in these patients, it should be used with caution because of the hepatic metabolism and renal excretion of fentanyl.

Patients with Fever/External Heat

Based on a pharmacokinetic model, serum fentanyl concentrations could theoretically increase by approximately one third for patients with a body temperature of 40°C (104°F) due to temperature-dependent increases in fentanyl release from the system and increased skin permeability. Therefore, patients wearing DURAGESIC® systems who develop fever should be monitored for opioid side effects and the DURAGESIC® dose should be adjusted if necessary.

ALL PATIENTS AND THEIR CAREGIVERS SHOULD BE ADVISED TO AVOID EXPOSING THE DURAGESIC® APPLICATION SITE TO DIRECT EXTERNAL HEAT SOURCES, SUCH AS HEATING PADS OR ELECTRIC BLANKETS, HEAT LAMPS, SAUNAS, HOT TUBS, AND HEATED WATER BEDS, ETC., WHILE WEARING THE SYSTEM. THERE IS A POTENTIAL FOR TEMPERATURE-DEPENDENT INCREASES IN FENTANYL RELEASE FROM THE SYSTEM.

Drug Interactions

Central Nervous System Depressants

When patients are receiving DURAGESIC®, the dose of additional opioids or other CNS depressant drugs (including benzodiazepines) should be reduced by at least 50%. With the concomitant use of CNS depressants, hypotension may occur.

Agents Affecting Cytochrome P450 3A4 Isoenzyme System

CYP3A4 Inhibitors: Since the metabolism of fentanyl is mediated by the CYP3A4 isozyme, coadministration of drugs that inhibit CYP3A4 activity may cause decreased clearance of fentanyl. The expected clinical results would be increased or prolonged opioid effects. Thus patients coadministered with inhibitors of CYP3A4 such as macrolide antibiotics (e.g., erythromycin), azole antifungal agents (e.g., ketoconazole), and protease inhibitors (e.g., ritanovir) while receiving DURAGESIC® should be carefully monitored and dosage adjustment made if warranted.

CYP3A4 Inducers: Cytochrome P450 inducers, such as rifampin, carbamazepine, and phenytoin, induce metabolism and as such may cause increased clearance of fentanyl. Caution is advised when administering DURAGESIC® to patients receiving these medications and if necessary dose adjustments should be considered.

Drug or Alcohol Dependence

Use of DURAGESIC® in combination with alcoholic beverages and/or other CNS depressants can result in increased risk to the patient. DURAGESIC® should be used with caution in individuals who have a history of drug or alcohol abuse, especially if they are outside a medically controlled environment.

Ambulatory Patients

Strong opioid analgesics impair the mental or physical abilities required for the performance of potentially dangerous tasks such as driving a car or operating machinery. Patients who have been given DURAGESIC® should not drive or operate dangerous machinery unless they are tolerant to the effects of the drug.

Carcinogenesis, Mutagenesis, and Impairment of Fertility

Because long-term animal studies have not been conducted, the potential carcinogenic effects of DURAGESIC® are unknown. There was no evidence of mutagenicity in the Ames *Salmonella typhimurium* mutagenicity assay, the primary rat hepatocyte unscheduled DNA synthesis assay, the BALB/c-3T3 transformation test, the mouse lymphoma assay, the human lymphocyte and CHO chromosomal aberration in-vitro assays, or the in-vivo micronucleus test.

Pregnancy – Pregnancy Category C

Fentanyl has been shown to impair fertility and to have an embryocidal effect in rats when given in intravenous doses 0.3 times the human dose for a period of 12 days. No evidence of teratogenic effects has been observed after administration of fentanyl to rats. There are no adequate and well-controlled studies in pregnant women. DURAGESIC® should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery

DURAGESIC® is not recommended for analgesia during labor and delivery.

Nursing Mothers

Fentanyl is excreted in human milk; therefore DURAGESIC® is not recommended for use in nursing women because of the possibility of effects in their infants.

Pediatric Use

DURAGESIC® was not studied in children under 2 years of age. DURAGESIC® should be administered to children only if they are opioid tolerant and age 2 years or older (See DOSAGE AND ADMINISTRATION and BOX WARNING).

To guard against accidental ingestion by children, use caution when choosing the application site for DURAGESIC® (See DOSAGE and ADMINISTRATION) and monitor adhesion of the system closely.

Geriatric Use

Information from a pilot study of the pharmacokinetics of IV fentanyl in geriatric patients indicates that the clearance of fentanyl may be greatly decreased in the population above the age of 60. The relevance of these findings to transdermal fentanyl is unknown at this time.

Since elderly, cachectic, or debilitated patients may have altered pharmacokinetics due to poor fat stores, muscle wasting, or altered clearance, they should not be started on DURAGESIC® doses higher than 25 µg/h unless they are already taking more than 135 mg of oral morphine a day or an equivalent dose of another opioid (see DOSAGE AND ADMINISTRATION).

Information for Patients

A patient instruction sheet is included in the package of DURAGESIC® systems dispensed to the patient.

Disposal of DURAGESIC®

DURAGESIC® should be kept out of the reach of children. DURAGESIC® systems should be folded so that the adhesive side of the system adheres to itself, then the system should be flushed down the toilet immediately upon removal. Patients should dispose of any systems remaining from a prescription as soon as they are no longer needed. Unused systems should be removed from their pouches and flushed down the toilet.

IF THE GEL FROM THE DRUG RESERVOIR ACCIDENTALLY CONTACTS THE SKIN, THE AREA SHOULD BE WASHED WITH CLEAR WATER.

ADVERSE REACTIONS

In post-marketing experience, deaths from hypoventilation due to inappropriate use of DURAGESIC® (fentanyl transdermal system) have been reported. (See BOX WARNING and CONTRAINDICATIONS.)

Pre-marketing Clinical Trial Experience:

In adults, the safety of DURAGESIC® has been evaluated in 357 postoperative patients and 153 cancer patients for a total of 510 patients. Patients with acute pain used DURAGESIC® for 1 to 3 days. The duration of DURAGESIC® use varied in cancer patients; 56% of patients used DURAGESIC® for over 30 days, 28% continued treatment for more than 4 months, and 10% used DURAGESIC® for more than 1 year.

HYPOVENTILATION WAS THE MOST SERIOUS ADVERSE REACTION OBSERVED IN 13 (4%) POSTOPERATIVE PATIENTS AND IN 3 (2%) OF THE CANCER PATIENTS. HYPOTENSION AND HYPERTENSION WERE OBSERVED IN 11 (3%) AND 4 (1%) OF THE OPIOID-NAIVE PATIENTS.

Various adverse events were reported; a causal relationship to DURAGESIC® was not always determined. The frequencies presented here reflect the actual frequency of each adverse effect in patients who received DURAGESIC®. There has been no attempt to correct for a placebo effect, concomitant use of other opioids, or to subtract the frequencies reported by placebo-treated patients in controlled trials.

Adverse reactions reported in 153 cancer patients at a frequency of 1% or greater are presented in Table 1; similar reactions were seen in the 357 postoperative patients studied.

In the pediatric population, the safety of DURAGESIC® has been evaluated in 291 patients ages 2-18 years with chronic pain. The duration of DURAGESIC® use varied; 20% of pediatric patients were treated for ≤ 15 days; 46% for 16-30 days; 16% for 31-60 days; and 17% for at least 61 days. Twenty-five patients were treated with DURAGESIC® for at least 4 months and 9 patients for more than 9 months.

There was no apparent pediatric-specific risk associated with DURAGESIC® use in children as young as 2 years old when used as directed.

The most common adverse events were fever (35%), vomiting (33%), and nausea (24%).

Adverse events reported in pediatric patients at a rate of ≥ 1% are presented in Table 1.

TABLE 1: ADVERSE EVENTS (at rate of ≥ 1%)
Adult (N=153) and Pediatric (N=291) Pre-Marketing Clinical Trial Experience

Body System	**Adults**	**Pediatrics**
Body as a Whole	Abdominal pain*, headache*	Pain*, headache*, fever, syncope, abdominal pain, allergic reaction, flushing
Cardiovascular	Arrhythmia, chest pain	Hypertension, tachycardia
Digestive	Nausea**, vomiting**, constipation**, dry mouth**, anorexia*, diarrhea*, dyspepsia*, flatulence	Nausea**, vomiting**, constipation*, dry mouth, diarrhea
Nervous	Somnolence**, confusion**, asthenia**, dizziness*, nervousness*, hallucinations*, anxiety*, depression*, euphoria*, tremor, abnormal coordination, speech disorder, abnormal thinking, abnormal gait, abnormal dreams, agitation, paresthesia, amnesia, syncope, paranoid reaction	Somnolence*, nervousness*, insomnia*, asthenia*, hallucinations, anxiety, depression, convulsions, dizziness, tremor, speech disorder, agitation, stupor, confusion, paranoid reaction
Respiratory	Dyspnea*, hypoventilation*, hemoptysis, pharyngitis, hiccups	Dyspnea, respiratory depression, rhinitis, coughing
Skin and Appendages	Sweating**, pruritus*, rash, application site reaction – erythema, papules, itching, edema.	Pruritus*, application site reaction*, sweating increased, rash, rash erythematous, skin reaction localized
Urogenital	Urinary retention*	Urinary retention

* Reactions occurring in 3% - 10% of DURAGESIC® patients
** Reactions occurring in 10% or more of DURAGESIC® patients

The following adverse effects have been reported in less than 1% of the 510 adult postoperative and cancer patients studied; the association between these events and DURAGESIC® administration is unknown. This information is listed to serve as alerting information for the physician.

Cardiovascular: bradycardia
Digestive: abdominal distention
Nervous: aphasia, hypertonia, vertigo, stupor, hypotonia, depersonalization, hostility
Respiratory: stertorous breathing, asthma, respiratory disorder
Skin and Appendages, General: exfoliative dermatitis, pustules

Special Senses: amblyopia
Urogenital: bladder pain, oliguria, urinary frequency

Post-Marketing Experience- Adults:
The following adverse reactions reported to have been observed in association with the use of DURAGESIC® and not reported in the pre-marketing adverse reactions section above include:

Body as a Whole: edema
Cardiovascular: tachycardia
Metabolic and Nutritional: weight loss
Special Senses: blurred vision

DRUG ABUSE AND DEPENDENCE

Fentanyl is a Schedule II controlled substance and can produce drug dependence similar to that produced by morphine. DURAGESIC® (fentanyl transdermal system) therefore has the potential for abuse. Tolerance, physical and psychological dependence may develop upon repeated administration of opioids. Iatrogenic addiction following opioid administration is relatively rare. Physicians should not let concerns of physical dependence deter them from using adequate amounts of opioids in the management of severe pain when such use is indicated.

OVERDOSAGE

Clinical Presentation
The manifestations of fentanyl overdosage are an extension of its pharmacologic actions with the most serious significant effect being hypoventilation.

Treatment
For the management of hypoventilation immediate countermeasures include removing the DURAGESIC® (fentanyl transdermal system) system and physically or verbally stimulating the patient. These actions can be followed by administration of a specific narcotic antagonist such as naloxone. The duration of hypoventilation following an overdose may be longer than the effects of the narcotic antagonist's action (the half-life of naloxone ranges from 30 to 81 minutes). The interval between IV antagonist doses should be carefully chosen because of the possibility of re-narcotization after system removal; repeated administration of naloxone may be necessary. Reversal of the narcotic effect may result in acute onset of pain and the release of catecholamines.

If the clinical situation warrants, ensure a patent airway is established and maintained, administer oxygen and assist or control respiration as indicated and use an oropharyngeal airway or endotracheal tube if necessary. Adequate body temperature and fluid intake should be maintained.

If severe or persistent hypotension occurs, the possibility of hypovolemia should be considered and managed with appropriate parenteral fluid therapy.

DOSAGE AND ADMINISTRATION

With all opioids, the safety of patients using the products is dependent on health care practitioners prescribing them in strict conformity with their approved labeling with respect to patient selection, dosing, and proper conditions for use.

As with all opioids, dosage should be individualized. The most important factor to be considered in determining the appropriate dose is the extent of pre-existing opioid tolerance. (See BOX WARNING and CONTRAINDICATIONS.) Initial doses should be reduced in elderly or debilitated patients (see PRECAUTIONS).

DURAGESIC® (fentanyl transdermal system) should be applied to non-irritated and non-irradiated skin on a flat surface such as chest, back, flank or upper arm. In young children, adhesion should be monitored and the upper back is the preferred location to minimize the potential of the child removing the patch. Hair at the application site should be clipped (not shaved) prior to system application. If the site of DURAGESIC® application must be cleansed prior to application of the system, do so with clear water. Do not use soaps, oils, lotions, alcohol, or any other agents that might irritate the skin or alter its characteristics. Allow the skin to dry completely prior to system application.

DURAGESIC® should be applied immediately upon removal from the sealed package. Do not alter the system (eg, cut) in any way prior to application.

The transdermal system should be pressed firmly in place with the palm of the hand for 30 seconds, making sure the contact is complete, especially around the edges.

Each DURAGESIC® may be worn continuously for 72 hours. If analgesia for more than 72 hours is required, a new system should be applied to a different skin site after removal of the previous transdermal system.

DURAGESIC® should be kept out of the reach of children. Used systems should be folded so that the adhesive side of the system adheres to itself, then the system should be flushed down the toilet immediately upon removal. Patients should dispose of any systems remaining from a prescription as soon as they are no longer needed. Unused systems should be removed from their pouches and flushed down the toilet.

Dose Selection

DOSES MUST BE INDIVIDUALIZED BASED UPON THE STATUS OF EACH PATIENT AND SHOULD BE ASSESSED AT REGULAR INTERVALS AFTER DURAGESIC® APPLICATION. REDUCED DOSES OF DURAGESIC® ARE SUGGESTED FOR THE ELDERLY AND OTHER GROUPS DISCUSSED IN PRECAUTIONS.

DURAGESIC® DOSES GREATER THAN 25 µG/H SHOULD NOT BE USED FOR INITIATION OF DURAGESIC® THERAPY IN NON-OPIOID-TOLERANT PATIENTS. Pediatric patients converting to Duragesic therapy with a 25 µg/h patch should be opioid-tolerant and receiving at least 45 mg oral morphine equivalents per day. The dose-conversion schedule described in Table C and method of titration described below were used safely in opioid-tolerant pediatric patients over the age of 2 years with chronic pain (See Precautions-Pediatric use)

In selecting an initial DURAGESIC® dose, attention should be given to 1) the daily dose, potency, and characteristics of the opioid the patient has been taking previously (eg, whether it is a pure agonist or

mixed agonist-antagonist), 2) the reliability of the relative potency estimates used to calculate the DURAGESIC® dose needed (potency estimates may vary with the route of administration), 3) the degree of opioid tolerance, if any, and 4) the general condition and medical status of the patient. Each patient should be maintained at the lowest dose providing acceptable pain control.

Initial DURAGESIC® Dose Selection

There has been no systematic evaluation of DURAGESIC® as an initial opioid analgesic in the management of chronic pain, since most patients in the clinical trials were converted to DURAGESIC® from other narcotics. Therefore, unless the patient has pre-existing opioid tolerance, the lowest DURAGESIC® dose, 25 µg/h, should be used as the initial dose.

To convert adult and pediatric patients from oral or parenteral opioids to DURAGESIC® use the following methodology:

1. Calculate the previous 24-hour analgesic requirement.

2. Convert this amount to the equianalgesic oral morphine dose using Table C.

3. Table D displays the range of 24-hour oral morphine doses that are recommended for conversion to each DURAGESIC® dose. Use this table to find the calculated 24-hour morphine dose and the corresponding DURAGESIC® dose. Initiate DURAGESIC® treatment using the recommended dose and titrate patients upwards (no more frequently than every 3 days after the initial dose or than every 6 days thereafter) until analgesic efficacy is attained. The recommended starting dose when converting from other opioids to DURAGESIC® is likely too low for 50% of patients. This starting dose is recommended to minimize the potential for overdosing patients with the first dose. For delivery rates in excess of 100 µg/h, multiple systems may be used.

Table C[a]
EQUIANALGESIC POTENCY CONVERSION

Name	Equianalgesic Dose (mg) IM[b,c]	PO
Morphine	10	60 (30)[d]
Hydromorphone (Dilaudid®)	1.5	7.5
Methadone (Dolophine®)	10	20
Oxycodone	15	30
Levorphanol (Levo-Dromoran®)	2	4
Oxymorphone (Numorphan®)	1	10 (PR)
Meperidine (Demerol®)	75	—
Codeine	130	200

[a] All IM and PO doses in this chart are considered equivalent to 10 mg of IM morphine in analgesic effect. IM denotes intramuscular, PO oral, and PR rectal.

[b] Based on single-dose studies in which an intramuscular dose of each drug listed was compared with morphine to establish the relative potency. Oral doses are those recommended when changing from parenteral to an oral route. Reference: Foley, K.M. (1985) The treatment of cancer pain. NEJM 313(2):84-95.

[c] Although controlled studies are not available, in clinical practice it is customary to consider the doses of opioid given IM, IV or subcutaneously to be equivalent. There may be some differences in pharmacokinetic parameters such as C_{max} and T_{max}.

[d] The conversion ratio of 10 mg parenteral morphine = 30 mg oral morphine is based on clinical experience in patients with chronic pain. The conversion ratio of 10 mg parenteral morphine = 60 mg oral morphine is based on a potency study in acute pain. Reference: Ashburn and Lipman (1993) Management of pain in the cancer patient. Anesth Analg 76:402-416.

Table D[1]
RECOMMENDED INITIAL DURAGESIC® DOSE BASED UPON DAILY ORAL MORPHINE DOSE

Oral 24-hour Morphine (mg/day)	DURAGESIC® Dose (µg/h)
45-134[2]	25
135-224	50
225-314	75
315-404	100
405-494	125
495-584	150
585-674	175
675-764	200
765-854	225
855-944	250
945-1034	275
1035-1124	300

NOTE: In clinical trials these ranges of daily oral morphine doses were used as a basis for conversion to DURAGESIC®.

[1] THIS TABLE SHOULD NOT BE USED TO CONVERT FROM DURAGESIC® TO OTHER THERAPIES, BECAUSE THIS CONVERSION TO DURAGESIC® IS CONSERVATIVE. USE OF TABLE D FOR CONVERSION TO OTHER ANALGESIC THERAPIES CAN OVERESTIMATE THE DOSE OF THE NEW AGENT. OVERDOSAGE OF THE NEW ANALGESIC AGENT IS POSSIBLE. (See DOSAGE AND ADMINISTRATION - Discontinuation of DURAGESIC®.)

[2] PEDIATRIC PATIENTS INITIATING THERAPY ON A 25 µG/H DURAGESIC® SYSTEM SHOULD BE OPIOID-TOLERANT AND RECEIVING AT LEAST 45 MG ORAL MORPHINE EQUIVALENTS PER DAY.

The majority of patients are adequately maintained with DURAGESIC® administered every 72 hours. A small number of patients may not achieve adequate analgesia using this dosing interval and may require systems to be applied every 48 hours rather than every 72 hours. An increase in the DURAGESIC® dose should be evaluated before changing dosing intervals in order to maintain patients on a 72-hour regimen. Dosing intervals less than every 72 hours were not studied in children and adolescents and are not recommended.

Because of the increase in serum fentanyl concentration over the first 24 hours following initial system application, the initial evaluation of the maximum analgesic effect of DURAGESIC® cannot be made before 24 hours of wearing. The initial DURAGESIC® dosage may be increased after 3 days (see Dose Titration).

During the initial application of DURAGESIC®, patients should use short-acting analgesics as needed until analgesic efficacy with DURAGESIC® is attained. Thereafter, some patients still may require periodic supplemental doses of other short-acting analgesics for 'breakthrough' pain.

Dose Titration

The recommended initial DURAGESIC® dose based upon the daily oral morphine dose is conservative, and 50% of patients are likely to require a dose increase after initial application of DURAGESIC®. The initial DURAGESIC® dosage may be increased after 3 days based on the daily dose of supplemental analgesics required by the patient in the second or third day of the initial application.

Physicians are advised that it may take up to 6 days after increasing the dose of DURAGESIC® for the patient to reach equilibrium on the new dose (see graph in CLINICAL PHARMACOLOGY). Therefore, patients should wear a higher dose through two applications before any further increase in dosage is made on the basis of the average daily use of a supplemental analgesic.

Appropriate dosage increments should be based on the daily dose of supplementary opioids, using the ratio of 90 mg/24 hours of oral morphine to a 25 µg/h increase in DURAGESIC® dose.

Discontinuation of DURAGESIC®

To convert patients to another opioid, remove DURAGESIC® and titrate the dose of the new analgesic based upon the patient's report of pain until adequate analgesia has been attained. Upon system removal, 17 hours or more are required for a 50% decrease in serum fentanyl concentrations. Opioid withdrawal symptoms (such as nausea, vomiting, diarrhea, anxiety, and shivering) are possible in some patients after conversion or dose adjustment. For patients requiring discontinuation of opioids, a gradual downward titration is recommended since it is not known at what dose level the opioid may be discontinued without producing the signs and symptoms of abrupt withdrawal.

TABLE D SHOULD NOT BE USED TO CONVERT FROM DURAGESIC® TO OTHER THERAPIES. BECAUSE THE CONVERSION TO DURAGESIC® IS CONSERVATIVE, USE OF TABLE D FOR CONVERSION TO OTHER ANALGESIC THERAPIES CAN OVERESTIMATE

THE DOSE OF THE NEW AGENT. OVERDOSAGE OF THE NEW ANALGESIC AGENT IS POSSIBLE.

HOW SUPPLIED

DURAGESIC® (fentanyl transdermal system) is supplied in cartons containing 5 individually packaged systems. See chart for information regarding individual systems.

DURAGESIC® Dose (µg/h)	System Size (cm^2)	Fentanyl Content (mg)	NDC Number
DURAGESIC®-25	10	2.5	50458-033-05
DURAGESIC®-50*	20	5	50458-034-05
DURAGESIC®-75*	30	7.5	50458-035-05
DURAGESIC®-100*	40	10	50458-036-05

*FOR USE ONLY IN OPIOID TOLERANT PATIENTS.

Safety and Handling

DURAGESIC® is supplied in sealed transdermal systems which pose little risk of exposure to health care workers. If the gel from the drug reservoir accidentally contacts the skin, the area should be washed with copious amounts of water. Do not use soap, alcohol, or other solvents to remove the gel because they may enhance the drug's ability to penetrate the skin. Do not cut or damage DURAGESIC®. If the DURAGESIC® system is cut or damaged, controlled drug delivery will not be possible.

KEEP DURAGESIC® OUT OF THE REACH OF CHILDREN

Do not store above 77°F (25°C). Apply immediately after removal from individually sealed package. Do not use if the seal is broken. **For transdermal use only.**

Rx only

DEA ORDER FORM REQUIRED. A SCHEDULE CII NARCOTIC.

MANUFACTURED BY:
ALZA Corporation,
Mountain View, CA 94043

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DISTRIBUTED BY:
JANSSEN PHARMACEUTICA PRODUCTS, L.P.
TITUSVILLE, NJ 08560

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Patient Information

DURAGESIC®
(FENTANYL TRANSDERMAL SYSTEM) CII

This leaflet contains important information about DURAGESIC® (Dur-ah-GEE-zik). Read this Patient Information carefully before you start using DURAGESIC®. Read it each time you get a prescription. There may be new information. This information does not take the place of talking to your health care provider about your medical condition or your treatment. Only your health care provider can decide if DURAGESIC® is the right treatment for you. If you do not understand some of this information or have questions, talk with your health care provider.

What is the most important information I should know about DURAGESIC®?

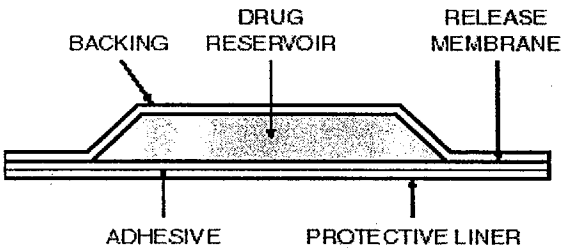
- **Only use DURAGESIC® the way your health care provider recommends.**
- **DURAGESIC® contains fentanyl, a narcotic pain medicine that if taken the wrong way can lead to serious problems, including overdose and death.**
- **DURAGESIC® should only be used to treat chronic (continuing) pain that is moderate to severe**

  –When strong pain medicines are needed, and
  –When pain medicine is needed around the clock (all the time)

- **DURAGESIC® should not be used to treat pain that will last only a few days.** This includes the pain that happens with surgery, medical, or dental procedures.
- **DURAGESIC® should only be used in children age 2 years or older who are already using other narcotic pain medicines (opioid tolerant).** DURAGESIC® has not been studied in children who are less than 2 years of age. It is not known if DURAGESIC® would be safe in these children.
- **Only use DURAGESIC® for the condition for which it was prescribed.**

What is DURAGESIC®?

DURAGESIC® is a prescription medicine that contains fentanyl. DURAGESIC® is a controlled substance (CII) because it is a strong narcotic pain medicine (opioid). DURAGESIC® is a thin, adhesive, rectangular patch that is worn on your skin. It has enough medicine to last for up to 3 days. The medicine passes through your skin and into your body. DURAGESIC® is used to treat moderate to severe pain that is expected to last for more than a few days.



Who should not use DURAGESIC®?

Do not use DURAGESIC®;

- For pain that will go away in a few days
- For pain from surgery, medical or dental procedures
- Unless strong pain medicines are needed
- If you are allergic to fentanyl
- In children who are less than 2 years old
- In children 2 years or older who are not already using other narcotic pain medicines

Before using DURAGESIC®, tell your health care provider if you:

- **Are pregnant or planning to become pregnant.** DURAGESIC® may harm your unborn baby.
- **Are breast feeding.** The medicine in DURAGESIC® passes into your milk and can harm your baby.
- **Have trouble breathing or lung problems**
- **Have a head injury or brain problems**
- **Have a heart problem called bradycardia (slow heart beat)**
- **Have liver problems**
- **Have kidney problems**
- **Have a history of drug or alcohol abuse**
- **Have skin reactions to adhesives (glues) used in** DURAGESIC®. See the end of this leaflet for a complete list of all the ingredients in DURAGESIC®.

Some medicines may cause serious side effects when used with DURAGESIC®. Tell your health care provider about all the medicines you take including prescription and non-prescription

medicines, vitamins, and herbal supplements. Sometimes, the doses of certain medicines and DURAGESIC® need to be changed when used together.

What should I know about using DURAGESIC® in children?

- DURAGESIC® can be used in children 2 years or older only if they are opioid-tolerant. These are children who are using other narcotic pain medicines for continuing pain right before starting DURAGESIC®.
- DURAGESIC® has not been studied in children who are less than 2 years old. It is not known if it would be safe in these children.
- In young children, put the patch on the upper back. This will lower the chances that the child will remove the patch and put it in their mouth.
- Keep this medicine in a safe place. Keep DURAGESIC® out of the reach of children.

How do I use DURAGESIC®?

- Follow your health care provider's directions exactly. Your health care provider may change your dose based on your reactions to the medicine. Do not change your dose or stop using DURAGESIC® unless your health care provider tells you to. Do not use DURAGESIC® more often than prescribed. (See the end of this leaflet for "How and when to apply DURAGESIC®.")
- Do not wear more than **one** DURAGESIC® patch at a time, unless your health care provider tells you to do so.
- Call your health care provider right away if you get a fever higher than 102°F. A fever may cause too much of the medicine in DURAGESIC® to pass into your body. Your health care provider may tell you to use a lower dose while you have a fever.
- If you use too much DURAGESIC® or overdose, get emergency medical help right away.
- If you have concerns about addiction when using your pain medicine or if you have experienced drug or alcohol addiction in the past, talk to your health care provider.
- After you have stopped using a patch, be sure to fold the sticky sides of the patch together and flush it down the toilet. Do not put used DURAGESIC® patches in a garbage can.
- If your health care provider tells you to stop using DURAGESIC®, throw away the unused packages. Open the unused packages and fold the sticky sides of the patches together, and flush them down the toilet.

What should I avoid while using DURAGESIC®?

- **Do not use heat sources such as heating pads, electric blankets, heat lamps, saunas, hot tubs, or heated waterbeds. Do not take long hot baths or sun bathe.** All of these can make your temperature rise and cause too much of the medicine in DURAGESIC® to pass into your body.

- **Do not breast feed unless your health care provider tells you it is okay.** DURAGESIC® passes into your milk and can cause serious problems for your baby.

- **Do not take other medicines without talking to your health care provider.** Other medicines include prescription and non-prescription medicines, vitamins, and herbal supplements. **Be especially careful about other medicines that make you sleepy.**

- **DO NOT DRINK ANY ALCOHOL WHILE USING DURAGESIC®.** IT CAN INCREASE YOUR CHANCES OF HAVING DANGEROUS SIDE EFFECTS.

- **DO NOT DRIVE, OPERATE HEAVY MACHINERY, OR DO OTHER POSSIBLY DANGEROUS ACTIVITIES** UNTIL YOU KNOW HOW DURAGESIC® AFFECTS YOU. DURAGESIC® CAN MAKE YOU SLEEPY. ASK YOUR HEALTH CARE PROVIDER TO TELL YOU WHEN IT IS OKAY TO DO THESE ACTIVITIES.

- **DO NOT STOP USING DURAGESIC® SUDDENLY.** YOUR BODY CAN DEVELOP A PHYSICAL DEPENDENCE ON DURAGESIC®. YOU CAN GET SICK IF YOU SUDDENLY STOP USING IT. TALK TO YOUR HEALTH CARE PROVIDER ABOUT HOW TO SAFELY STOP USING DURAGESIC®.

What are the possible side effects of DURAGESIC®?

- **DURAGESIC® can cause trouble breathing (hypoventilation) which can be dangerous and even lead to death if not treated.** This can happen if you use too much DURAGESIC® or the dose is too high for you. The signs and symptoms of hypoventilation include:
  –Slow breathing
  –Shallow breathing (little chest movement with breathing)
  –Trouble breathing

Call your health care provider right away or get emergency medical help if you have trouble breathing or have other serious side effects while using DURAGESIC®.

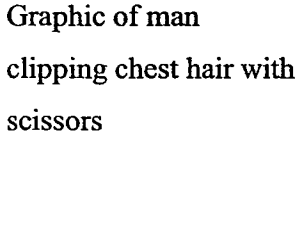
- The most common side effects with DURAGESIC® are nausea, vomiting, constipation, dry mouth, sleepiness, confusion, weakness, and sweating. Although uncommon, trouble sleeping and seizures were reported in children. These are not all the possible side effects of DURAGESIC®. For a complete list, ask your health care provider or pharmacist.

- Talk to your health care provider about any side effect that concerns you.

How and where to apply DURAGESIC®

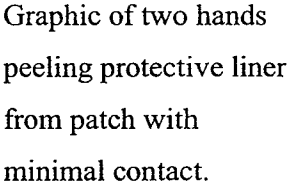
IN THE HOSPITAL, YOUR HEALTH CARE PROVIDER OR OTHER MEDICAL PERSON WILL APPLY DURAGESIC® FOR YOU. AT HOME, YOU OR A MEMBER OF YOUR FAMILY MAY APPLY DURAGESIC® TO YOUR SKIN. YOU NEED TO CHECK THE PATCHES OFTEN TO MAKE SURE THAT THEY ARE STICKING WELL TO THE SKIN. IN YOUNG CHILDREN, PUT THE PATCH ON THE UPPER BACK. THIS WILL LOWER THE CHANCES THAT THE CHILD WILL REMOVE THE PATCH AND PUT IT IN THEIR MOUTH.

1. **Prepare:** For adults, put the patch on the chest, back, flank (sides of the waist), or upper arm in a place where there is no hair. Put it on right away after you have removed it from the pouch. Avoid sensitive areas or those that move around a lot. If there is hair, **do not shave (shaving irritates the skin).**

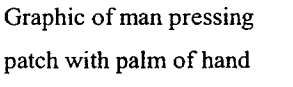

Graphic of man clipping chest hair with scissors

Instead, clip hair as close to the skin as possible. Clean the skin area with clear water **only**. **Pat skin completely dry.** Do not use anything on the skin (soaps, lotions, oils, alcohol, etc.) before the patch is applied.

2. **Peel:** Peel the liner from the back of the patch and throw away. **Touch the sticky side as little as possible.**


Graphic of two hands peeling protective liner from patch with minimal contact.

3. **Press:** Press the patch onto the skin **with the palm of your hand and hold there for a minimum of 30 seconds.** Make sure it sticks well, especially at the edges.


Graphic of man pressing patch with palm of hand

- Each DURAGESIC® patch is sealed in its own protective pouch. Do not remove the DURAGESIC® patch from the pouch until you are ready to use it. When you are ready to put on DURAGESIC®, tear open the pouch along the dotted line, starting at the slit, and remove the DURAGESIC® patch.

- Do not put the DURAGESIC® patch on skin that is very oily, burned, broken out, cut, irritated, or damaged in any way.

- If you have any questions about where on your body you should or should not apply the patch, please ask your health care provider.

- DURAGESIC® may not stick to all patients. If the patch does not stick well or comes lose after applying, tape the edges down with first aid tape. If the patch falls off, throw it away and put a new one on at a different skin site (see "Disposing of DURAGESIC®").

- Wash your hands when you have finished applying DURAGESIC®.

- Remove DURAGESIC® after wearing it for 3 days (see "Disposing of DURAGESIC®"). Choose a *different* place on the skin to apply a new DURAGESIC® patch and repeat Steps 1 through 3. **Do not apply the new patch to the same place as the last one.**

When to apply DURAGESIC®

- You can apply DURAGESIC® at any time of the day. Change it at about the same time of day 3 days later or as directed by your health care provider.
- Do not apply the new DURAGESIC® patch to the same place where you removed the last DURAGESIC® patch.
- Your health care provider may increase your DURAGESIC® dose if your pain is not controlled well. **If you continue to have pain, call your health care provider.**

Water and DURAGESIC®

You can bathe, swim or shower while you are wearing DURAGESIC®. If the patch falls off, put a new DURAGESIC® patch on your skin. Make sure the new skin area you have chosen is dry before putting on a new DURAGESIC® patch.

Disposing of DURAGESIC®

- BEFORE PUTTING ON A NEW DURAGESIC® PATCH, REMOVE THE PATCH YOU HAVE BEEN WEARING.

- FOLD THE USED DURAGESIC® PATCH IN HALF SO THAT THE STICKY SIDE STICKS TO ITSELF. **FLUSH THE USED DURAGESIC® DOWN THE TOILET RIGHT AWAY. A USED DURAGESIC® PATCH MAY BE DANGEROUS FOR OR EVEN LEAD TO DEATH IN BABIES, CHILDREN, PETS, AND ADULTS WHO HAVE NOT BEEN PRESCRIBED DURAGESIC®.**

- THROW AWAY ANY DURAGESIC® PATCHES THAT ARE LEFT OVER FROM YOUR PRESCRIPTION AS SOON AS THEY ARE NO LONGER NEEDED. REMOVE THE LEFTOVER PATCHES FROM THEIR PROTECTIVE POUCH AND REMOVE THE PROTECTIVE LINER. **FOLD THE PATCHES IN HALF WITH THE STICKY SIDES TOGETHER, AND FLUSH THE PATCHES DOWN THE TOILET.** DO NOT FLUSH THE POUCH OR THE PROTECTIVE LINER DOWN THE TOILET. THESE ITEMS CAN BE THROWN AWAY IN A GARBAGE CAN.

Safety and handling of DURAGESIC®

DURAGESIC® COMES IN SEALED PATCHES, WHICH WILL KEEP THE GEL FROM GETTING ON YOUR HANDS OR BODY. IF THE GEL FROM THE DRUG RESERVOIR ACCIDENTALLY CONTACTS THE SKIN, THE AREA SHOULD BE WASHED WITH LARGE AMOUNTS OF WATER. DO NOT USE SOAP, ALCOHOL, OR OTHER SOLVENTS TO REMOVE THE GEL BECAUSE THEY MAY INCREASE THE DRUG'S ABILITY TO GO THROUGH THE SKIN.

DO NOT CUT OR DAMAGE THE DURAGESIC® PATCH. DO NOT USE THE DURAGESIC® PATCH IF IT IS DAMAGED IN ANY WAY. DURAGESIC® WILL NOT WORK PROPERLY OR MAY NOT BE SAFE TO USE IF IT IS CUT OR DAMAGED. TOO MUCH MEDICINE MAY PASS TOO FAST INTO YOUR BODY IF THE PATCH IS DAMAGED.

THE PATCH MUST BE USED ONLY ON THE SKIN OF THE PERSON FOR WHOM IT WAS PRESCRIBED. IF THE PATCH COMES OFF AND ACCIDENTALLY STICKS TO THE SKIN OF ANOTHER PERSON, TAKE THE PATCH OFF OF THAT PERSON RIGHT AWAY AND CALL A HEALTH CARE PROVIDER OR POISON CONTROL CENTER.

PREVENT THEFT AND MISUSE. DURAGESIC® CONTAINS A NARCOTIC PAIN MEDICINE THAT CAN BE A TARGET FOR PEOPLE WHO ABUSE PRESCRIPTION MEDICINES. KEEP YOUR DURAGESIC® IN A SAFE PLACE, TO PROTECT IT FROM THEFT. NEVER GIVE DURAGESIC® TO ANYONE ELSE BECAUSE IT MAY BE DANGEROUS TO THEM. SELLING OR GIVING AWAY THIS MEDICINE IS AGAINST THE LAW.

How should DURAGESIC® be stored?

STORE DURAGESIC® BELOW 77° F (25° C). REMEMBER, THE INSIDE OF YOUR CAR CAN REACH TEMPERATURES MUCH HIGHER THAN THIS IN THE SUMMER.
KEEP DURAGESIC® IN ITS PROTECTIVE POUCH UNTIL YOU ARE READY TO USE IT.

GENERAL INFORMATION ABOUT THE SAFE AND EFFECTIVE USE OF DURAGESIC®

MEDICINES ARE SOMETIMES PRESCRIBED FOR CONDITIONS THAT ARE NOT MENTIONED IN PATIENT INFORMATION LEAFLETS. DO NOT USE DURAGESIC® FOR A CONDITION FOR WHICH IT WAS NOT PRESCRIBED. DO NOT GIVE DURAGESIC® TO OTHER

PEOPLE, EVEN IF THEY HAVE THE SAME SYMPTOMS YOU HAVE. IT MAY BE DANGEROUS FOR THEM, AND IT IS AGAINST THE LAW.

KEEP DURAGESIC® OUT OF THE REACH OF CHILDREN AND PETS.

This leaflet summarizes the most important information about DURAGESIC®. If you would like more information, talk with your health care provider. You can ask your health care provider or pharmacist for information about DURAGESIC® that is written for health professionals.

FOR QUESTIONS ABOUT DURAGESIC® CALL THE JANSSEN CUSTOMER ACTION CENTER AT 1-800-JANSSEN (1-800-526-7736) 9A.M. TO 5 P.M. EST, MONDAY THROUGH FRIDAY.

THIS PATIENT INFORMATION HAS BEEN APPROVED BY THE UNITED STATES FOOD AND DRUG ADMINISTRATION.

WHAT ARE THE INGREDIENTS OF DURAGESIC®?

ACTIVE INGREDIENT: FENTANYL

Inactive ingredients: alcohol*, ethylene-vinyl acetate copolymer membrane, hydroxyethyl cellulose, polyester film backing, silicone adhesive.

*Less than 0.2 mL of alcohol is released from the patch during use.

RX ONLY

MANUFACTURED BY:
ALZA CORPORATION
MOUNTAIN VIEW, CA 94043

DISTRIBUTED BY:
JANSSEN PHARMACEUTICA PRODUCTS, L.P.
TITUSVILLE, NJ 08560

JANSSEN
PHARMACEUTICA
PRODUCTS, L.P.

JANUARY 2003, MAY 2003 7500411

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-813 / S-036

SUMMARY REVIEW

EXECUTIVE SUMMARY OF CLINICAL AND CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEWS

Date of Submission:	**November 25, 2002**
Type of Submission:	**Supplement to NDA 19-813 for Pediatric Exclusivity Determination**
Product:	**DURAGESIC® (fentanyl transdermal system)**
Sponsor:	**ALZA**
Review Date:	**May 15, 2003**
Medical Team Leader:	**Sharon Hertz, M.D.**
Medical Officer:	**Dawn Elizabeth McNeil, M.D.**
Clinical Pharmacology and Biopharmaceutics Reviewer:	**David Lee, Ph.D.**
Pharmacometrics Consultant:	**He Sun, Ph.D.**
Project Manager:	**Kimberly Compton, Pharm.D.**

EXECUTIVE SUMMARY

DURAGESIC® (fentanyl transdermal patch, NDA 19-813) is an opioid analgesic that was originally approved in August 1990, for use in patients over the age of 12 years. DURAGESIC® is indicated for treatment of chronic pain (such as that of malignancy) that cannot be managed by lesser means such as acetaminophen-opioid combination, NSAIDs, or PRN dosing with short-acting opioids, and that requires continuous opioid administration.

The current supplement was submitted November 25, 2002 in response to a pediatric written request issued by the Agency on July 15, 1999 and amended on November 1, 1999 and February 22, 2001. The objectives of the written request were to evaluate the safety of initiating and continuing treatment with the fentanyl transdermal system in an opioid-tolerant pediatric patient population with chronic pain, to determine the pharmacokinetics of the fentanyl transdermal system in the same pediatric patient population, and to determine an appropriate dosing regimen.

The sponsor has met the objectives of the written request having demonstrated a safe method for converting patients to DURAGESIC from a prior opioid and a safe method for dose titration, and having provided an evaluation of the pharmacokinetics of DURAGESIC® in pediatric patients.

Dosing, titration, and safety information was obtained from Study FEN-USA-87, submitted to fulfill the requirements of the written request, with additional data from studies FEN-INT-24 and FEN-GBR-14. All three of these were open-label, two-week, multiple-dose studies of the safety and pharmacokinetics of DURAGESIC® in the pediatric patient population.

In Studies FEN-USA-87 and FEN-GBR-14 patients were converted to DURAGESIC® based on their opioid analgesic requirement over the previous 24 hours. In Study FEN-INT-24 all patients initiated therapy with an investigational DURAGESIC® patch at doses based on previous opoiod treatment. Titration in all studies was permitted every 72 hours as needed, based on use of rescue medication and pain assessments. Additional pharmacokinetic information was obtained from FEN-FRA-4, a single dose study in eight nonopioid tolerant patients.

As open-label studies, efficacy measures were incorporated only to provide descriptive information and in support of the dosing assessments.

Safety

The safety database consisted of 292 pediatric patients, distributed across the following age ranges: 2 < 6 (n = 66), 6 < 12 (n = 100), 12 < 16 (n = 117), and 16<18 (n=9). One hundred eighty-three patients received DURAGESIC for more than 16 days but fewer than 61 days. The vast majority of the pediatric patients had pain related to an underlying malignancy or its treatment.

None of the 94 deaths was clearly attributable to study drug. Over half of the subjects (57%) experienced at least one serious adverse event (SAE). Of the SAEs that could be attributed to study drug, none was unexpected for a product containing a potent opioid.

The most common adverse events were fever (35%), vomiting (33%) and nausea (23%). Three patients experienced respiratory depression within 96 hours of beginning Duragesic therapy. Two of the patients died, but there was no evidence to suggest a causal relationship between these deaths and the use of study medication. The third patient's decreased respiratory rate resolved after temporary discontinuation of the study drug.

Dosing

One hundred and forty-seven pediatric patients initiated therapy on a 25-µg/h patch. Ninety-four of these patients were receiving at least 90 mg oral morphine equivalents per day and 53 were receiving 45 to 89 mg oral morphine equivalents per day. The method of conversion from prior opioid to DURAGESIC® was well tolerated. Approximately 90% of the total daily opioid requirement (DURAGESIC® plus rescue medication) was provided by DURAGESIC®.

Forty-one percent of patients required dose titration with a mean of 5.6 days until the first dose titration was warranted. Of the 121 patients who received their first titration within the first two weeks, 45% required subsequent dose titration with an average time to subsequent titration of 3.8 days. The titration method, which increased DURAGESIC® by 25 µg/h for each 45 mg of morphine or equivalent opioid taken as rescue medication, was well tolerated.

Pharmacokinetics

The pharmacokinetic data submitted consists of a stand-alone pharmacokinetic study (FEN-FRA-04) and population pharmacokinetic analysis of data obtained from clinical studies FEN-USA-87 and FEN-INT-24.

Study FEN-FRA-04 documented that fentanyl plasma levels for 1.5 - 5 year old surgical patients were approximately twice as high as those for adult surgical patients. According to the population pharmacokinetic analysis, the pharmacokinetic profiles of fentanyl were similar for pediatric and adult patients.

Based on the safety experience obtained from the pediatric clinical trials, the proposed pediatric dosing regimen in the DOSAGE and ADMINISTRATION of the package insert has been recommended.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Bob Rappaport
5/20/03 05:23:46 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-813 / S-036

MEDICAL REVIEW(S)

CLINICAL REVIEW

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anesthetic, Critical Care, and Addiction Drug Products
HFD-170, Room 9B-45, 5600 Fishers Lane, Rockville MD 20857
Tel: (301) 827-7410

Medical Officer Review

Date of Submission:	**November 25, 2002**
Type of Submission:	**Supplement to NDA 19-813 for Pediatric Exclusivity Determination**
Product:	**Duragesic (fentanyl transdermal system)**
Sponsor:	**ALZA**
Review Date:	**April 30 2003**
Medical Officer:	**Dawn Elizabeth McNeil, M.D.**
Project Manager:	**Kimberly Compton**

Table of Contents

Clinical Review for NDA 19-813

Executive Summary

I. Recommendations

A. Recommendation on Approvability

I recommend approval of this supplement.

Duragesic (fentanyl transdermal patch, NDA 19-813) is an opioid analgesic approved for use in persons over the age of 12 years. The current indication is for the management of chronic pain in patients requiring continuous opioid analgesia. The efficacy of Duragesic for this indication was evaluated in the initial NDA submission, 19-813, approved in August 1990. This review evaluated the information presented in the pediatric supplement S036, submitted November 25 2002.

The Sponsor has submitted this supplemental NDA in response to a pediatric written request issued by the FDA.

The sponsor has met the objectives of the written request having demonstrated safe use of the product in pediatric patients as well as a safe and appropriate conversion method to Duragesic from oral and parenteral opioid therapies.

Patients safely initiated therapy with the 12.5 µg/h patch and the 25 µg/h patch. As a 12.5 µg/h patch has not been approved for use, pediatric patients requiring less than 45 mg/day of morphine or an equivalent dose of other opioid would not be appropriate candidates for use of Duragesic.

B. Recommendation on Phase 4 Studies and/or Risk Management Steps

The lowest strength has clear utility for initiating therapy in pediatric patients. The 12.5 µg/h strength and a dose of 125 µg/h may be confused. It is recommended that in the development of a 12.5 µg/h patch the sponsor should consider making the lowest strength patch distinctive to reduce the risk for error.

[redacted] nd pursue development of one of these latter patch dosages.

II. Summary of Clinical Findings

A. Brief Overview of Clinical Program

ALZA submitted a pediatric study request in 1999 to obtain changes to the following sections of the Duragesic label: BOXED WARNING, Clinical Pharmacology (pharmacokinetics subsection), Clinical trials, Precautions (pediatric use subsection), Adverse Reactions, and Dosage and Administration.

In response to this request, the Agency issued a pediatric written request (PWR) on July 15 1999.

Study FEN-USA-87 was submitted to fulfill the requirements of the written request: *A study to assess the safety, dose conversion and duration of Duragesic (fentanyl transdermal system) in pediatric subjects with chronic pain requiring opioid therapy.*

The Sponsor submitted safety data from FEN-USA-87, the protocol submitted to fulfill the requirements of the written request, with additional data from studies FEN-INT-24 and FEN-GBR-14. All three of these were open-label studies of the safety and pharmacokinetics of Duragesic in the pediatric patient population. FEN-USA-87, was an open-label, multi-center, single-arm, nonrandomized study in patients age 2 to 16 years. All of the pediatric patients had received previous opioid treatment for pain. The initial Duragesic dose was calculated based on the opioid analgesic requirement from the previous 24 hours, with titration every 72 hours as necessary. FEN-INT-24 was an open-label, multi-center, single-arm, nonrandomized study in patients age 2 to 12 years. An initial patch of 12.5 µg/h was to be placed on each subject, with replacement every 72 hours and titration as needed, based on use of rescue medication and pain assessments. FEN-GBR-14 was an open-label, multi-center, single-arm, nonrandomized study. The initial Duragesic dose was based on the opioid analgesic requirement from the previous 24 hours, with titration every 72 hours as necessary. Additional pharmacokinetic information was obtained from FEN-FRA-4, an open-label, single dose study in eight patients between the ages of one and five years.

The majority of the pediatric patients who participated in these studies were male (n=176, 60.1 %), and lived outside of the United States of America (n=177, 60.4%). The majority of patients enrolled in studies FEN-USA-87 and FEN-INT-24 were Caucasian, (n=156, 61.9%). No information on ethnicity was collected in FEN-GBR-14. Most of the pediatric patients were in the first decade of life, with a mean age of 9.7 years (range 1-16). Two one-year-olds were enrolled in violation of the protocol inclusion criteria, one of whom was included in the youngest age group (2<6 years old). Of the 241 pediatric patients for whom Tanner staging was assessed, most were preadolescent i.e. Tanner stage 1 (54.5% of females, 61.3% of males).

The majority of the pediatric patients (74%) had pain related to an underlying malignancy or its treatment. Pediatric patients with either pancreatitis (4%) or sickle cell disease

(4%) represented the next largest groups. Over 70% of the pediatric patients had nociceptive pain (n=189, 71.4%), with the remainder having either neuropathic pain (n=36, 14%) or multiple pain types (n=35, 14%).

B. Efficacy

These studies were all open-label studies without control arms. Efficacy measures were incorporated into the study design to provide descriptive information. The efficacy measures used were the Play Performance Scale (PPS) for evaluation of function, global assessments of pain treatment, pain intensity reporting and use of rescue medication. All of these measures trended towards improvement.

C. Safety

A total of 301 pediatric patients were treated with Duragesic. The eight patients who participated in the single-dose pharmacokinetic study, FEN-FRA-4, were not included in the safety database. The Integrated Summary of Safety (ISS) was based on the experiences of 293 pediatric patients, who received treatment for up to 15 days. Over half (n=234) participated in an extension period during which 172 pediatric patients received Duragesic for more than 16 days but fewer than 61 days and 18 pediatric patients remained on treatment for over 9 months.

With the exception of the 16-18 year old group in which only 44% completed the primary treatment period, over 75% of the pediatric patients per age group completed the study. During the initial treatment period, 38% of the withdrawals were due to death and 22% were due to insufficient response. During the extension phase, 25% of the withdrawals were due to deaths and 17% were due to insufficient response. There were no deaths clearly attributable to study medication.

Over half of the subjects (n=166, 57%) had at least one serious adverse event (SAE). Neoplasm was reported as an SAE in 46% of the pediatric patients who reported an SAE but did not represent a new event. Of the SAEs that could be attributed to study drug, none were unexpected for a product containing fentanyl.

The most common adverse events were fever (38%), vomiting (37%) and nausea (26%). The warning/precautions section of the current Duragesic label notes the theoretical concern that fever could enhance absorption of fentanyl from the patch. In this predominantly immunocompromised study population, while a fever incidence of 38% was noted, no correlation could be found between presence of fever and incidence of adverse effects.

Three patients experienced respiratory depression within 96 hours of beginning Duragesic therapy. Two of the patients died, but there was no evidence that suggested a

causal association between their deaths and the use of study medication. The third patient's decreased respiratory rate resolved after temporary discontinuation of the study drug.

The majority of the patients, 99.5%, were taking at least one other medication. The use of fentanyl in conjunction with CNS sedatives, antiemetic therapy, and/or chemotherapy was associated with a higher incidence of adverse events. These adverse events were generally associated with the reason for the concomitant medications i.e. nausea, vomiting and antiemetics or were known effects of the therapy i.e. nausea, vomiting and chemotherapy.

D. Dosing

Most pediatric patients began treatment with one of the two lowest Duragesic dosage strengths, 12.5 µg/h (an investigational formulation) or 25 µg/h. All patients in FEN-INT-24 started with an investigational formulation of 12.5 µg/h. Patients in FEN-GBR-14 had a minimum starting dose of 25 µg/h.

Patients in study FEN-USA-87 received an investigational formulation of 12.5 µg/h if they had a previous morphine equivalent dose of 30-44 mg. Patients in FEN-USA-87 who had a previous morphine equivalent requirement of 45-134 mg received an initial dose of 25 µg/h.

As there is not currently a 12.5 µg/h patch commercially available, patients requiring less than 45 mg of morphine or equivalent opioid medications are not appropriate candidates for Duragesic therapy.

In the primary treatment period, 41% (n=121) of the participants required dose titration with a mean of 5.6 days until the first dose titration was warranted. Of the 121 patients who received their first dose titration during the initial treatment period, 55 (45%) required subsequent dose titration with an average time to subsequent titration of 3.8 days. The titration method, which increased Duragesic by 25 µg/h for each 90 mg of morphine or equivalent opioid taken as rescue medication, was well tolerated.

E. Pharmacokinetics

The time to maximal concentration (T_{max}) was shorter in the pediatric subjects. The maximal plasma fentanyl concentration (C_{max}) was 54% higher in the pediatric population.

The elimination half-lives were shorter in the pediatric population than in the adult population. The FEN-FRA-4 study report suggested that the cutaneous depot effect may be less important in the pediatric population.

There was no correlation between fentanyl steady state concentration and adverse events such as nausea, vomiting, fever. In addition, there was no correlation between fentanyl steady state concentration and patient age, gender, race, or Tanner stage for sexual maturity. Alterations in body temperature, location of system application and administration of concomitant medications also had no effect on fentanyl concentrations. The analysis of concomitant medications specifically evaluated the effects of CYP3A4 inhibitors including cimetidine, erythromycin, fluconazole, metronidazole as well as the effects of CYP3A4 inducers such as phenobarbital, dexamethasone and phenytoin and found no effect.

Both steady state concentration and drug clearance were dependent on body surface area, study site and time from dosing. The sponsor reports that "an increase in BSA of 0.1 m^2 is predicted to result in a 4.8% increase in clearance and a 4.6% decrease in steady-state concentration."

F. Special Populations

- Gender

  There were no apparent gender-specific differences in the pharmacokinetics of fentanyl. The overall incidence of AEs was higher among male patients than female patients (94% versus 86%). Although the incidence of malignancy was equal at approximately 70%, a greater percentage of male patients on study USA-87 died (31% vs. 20%). There is no apparent explanation for this finding.

- Race/Ethnicity

  Fever, diarrhea, abdominal pain and nausea were all more common among US subjects and among Caucasians. While Black subjects had an AE incidence of 81%, all other ethnic groups had an AE incidence of greater than 90%. The incidence rates for death were similar for Caucasians, Blacks and Hispanics (29%, 25%, and 21% respectively).

- Other special categories, such as renal and hepatic insufficiency, were not specifically identified and evaluated. Adult patients were not eligible.

Medical Officer Date

Division Director Date

Clinical Review

I. Introduction and Background

A. Drug Established and Proposed Trade Name, Drug Class, Sponsor's Proposed Indication(s), Dose, Regimens, Age Groups

Duragesic (fentanyl transdermal patch, NDA 19-813), a synthetic phenylpiperidine opioid agonist, is currently approved for the management of chronic pain in patients requiring continuous opioid analgesia.

As a synthetic 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.

Duragesic permits transdermal administration of fentanyl with a dosing interval of 72 hours. The common side effects of Duragesic, as demonstrated in adults, include nausea, vomiting, constipation, somnolence, and diaphoresis. The most serious risk is respiratory depression.

The sponsor currently manufactures four dosage strengths (25 µg/h, 50µg/h, 75µg/h, 100µg/h) approved for use in patients 12 years old and older. The sponsor is not requesting a change in indication but rather is seeking to provide pediatric use information for patients aged 2 years and older.

B. State of Armamentarium for Indication(s)

Fentanyl is currently available in the US as an injectable formulation, as a transdermal patch, and as an oral lozenge. Morphine, hydromorphone, and oxycodone products, in varying formulations, are also marketed for use in patients with chronic pain requiring continuous opioid analgesia. There are no modified-release products approved for patients under twelve years old.

C. Important Milestones in Product Development

June 1984
IND 24, 417 was submitted

August 1990
Duragesic (NDA 19-813) was approved.

October 1998
A meeting was held with DACCADP to discuss proposed development for a lower dose DURAGESIC system and to discuss the requirements for pediatric exclusivity.

February 1999
Letter from DACCADP to ALZA requesting modifications to proposed pediatric study request. Specifically the Division requested inclusion of PK data as well as resolution of issues related to starting dose by age/weight, conversion/titration amounts and patch placement.

March 1999
ALZA submitted a revised pediatric study request.

July 1999

The Agency issued a Pediatric Written Request (PWR) for Duragesic. The requested study was to evaluate the safety and pharmacokinetics of Duragesic in children being treated for chronic pain, who had been using a minimum of 30 mg of oral morphine for one week prior to enrollment i.e. were considered opioid-tolerant. Two hundred children between the ages of two and sixteen years, at least 20% of whom would be appropriate for use of an initial patch size of 12.5 µg/h, should be studied. The PWR specifically stated that children under age 6 should be adequately represented in the study population. The PWR also specified requirements for an initial 72 hours of respiratory monitoring.

November 30 1999
Amendment #1 to the written request

- The number of study subjects was reduced to 150 from 200.
- The requirement for 20% of the subjects to receive an initial patch size of 12.5 µg/h was removed.
- The requirement for additional laboratory testing was removed.
- The submission date was extended from July 1 2001 to December 1 2001.

December 17 1999
Serial number 015 was submitted to IND —— *A study to assess the safety, dose conversion and duration of Duragesic (fentanyl transdermal system) in pediatric subjects with chronic pain requiring opioid therapy (FEN-USA-87).*

February 22 2001
Amendment #2 to the written request
Extension of the submission of pediatric data to "on or before December 1 2002" due to slow study enrollment

July 25 2002
ALZA sent the division an inquiry regarding the adequacy of study representation of children under six years old.

October 1 2002
The Division responded that pediatric patients under the age of six years were adequately represented

D. Other Relevant Information

Duragesic (Durogesic) is marketed in 57 countries and approved for marketing in 64 countries. This product has not been withdrawn from any market due to safety or efficacy concerns.

Duragesic is not currently approved for patients under 12 years old in any market, domestic or foreign.

E. Important Issues with Pharmacologically Related Agents

Drug-drug interactions have been identified with Fentanyl and drugs that inhibit cytochrome P450, isoenzyme 3A4.

II. Clinically Relevant Findings From Chemistry, Animal Pharmacology and Toxicology, Microbiology, Biopharmaceutics, Statistics and/or Other Consultant Reviews

No pre-clinical, chemistry or microbiology information was required by the PWR or submitted by the sponsor.

III. Description of Clinical Data and Sources

A. Overall Data

FEN-USA-87 was an open-label, multi-center, single-arm, nonrandomized study in patients age 2 to 16 years, submitted in support of safety and as part of the pooled multiple-dose pharmacokinetic database. All of the pediatric patients had received previous opioid treatment for pain. The initial Duragesic dose was calculated based on the opioid analgesic requirement from the previous 24 hours, with titration every 72 hours as needed.

FEN-INT-24 was an open-label, multi-center, single-arm, nonrandomized study in patients age 2 to 12 years submitted in support of safety and as part of the pooled multiple-dose pharmacokinetic database. An patch of 12.5 µg/h (investigational formulation) was placed on each subject, with titration every 72 hours as needed, based on use of rescue medication and pain assessments.

FEN-GBR-14 was an open-label, multi-center, single-arm, nonrandomized study submitted in support of safety. The initial Duragesic dose was based on the opioid analgesic requirement from the previous 24 hours, with titration every 72 hours as needed.

FEN-FRA-4 was an open-label, multi-center, single–arm, nonrandomized pharmacokinetic study in pediatric surgical patients aged between 18 months and 5 years submitted as single-dose pharmacokinetic data.

In total 302 pediatric patients were enrolled in the four studies. One child never received any treatment and was not included in the exposed population (FEN-USA-87). The eight pediatric patients who participated in FEN-FRA-4 were not included in the Integrated Summary of Safety (ISS). As a result the ISS was based on the experiences of 293 pediatric patients

FEN-USA-87:
This study began in March 2000 and is ongoing.

Title: A study to assess the safety, dose conversion and duration of Duragesic (fentanyl transdermal system) in pediatric subjects with chronic pain requiring opioid therapy

Objective: Evaluate the safety, dose conversion and titration of Duragesic in pediatric subjects

Population: 200 pediatric patients with at least a one week history of chronic pain requiring scheduled opioids. Subjects were to be enrolled in three age cohorts, a) 2 years to <6 years, b) 6 years to <12 years and c) 12 years to <16 years. Cohorts a and b was to enroll 40 patients each. Cohort c was to enroll 80 patients.

Key Inclusion Criteria:

1. Male or female subjects at least 2 and < 16 years of age with chronic pain of a well documented etiology requiring around the clock opioids who are willing to be hospitalized for the first 48-72 hours of Duragesic treatment. (This criteria was modified to allow home use under supervision, amendment V to the protocol dated 13 November 2000. When at-home subjects would be under constant supervision during the initial 72 hours.)
2. Subjects must have been receiving scheduled opioids for a minimum of 7 days prior to enrollment with a projected need for scheduled opioids for at least the length of the primary 15-day treatment period.
3. Subjects must have been receiving the equivalent of at least 30 mg of oral morphine/day prior to enrollment

Key Exclusion Criteria:

1. Skin disease that could preclude the use of the transdermal system or that could affect local tolerability or fentanyl absorption

2. Known sensitivity to fentanyl, other opioids or adhesives
3. Febrile subjects could be enrolled but serum fentanyl concentrations may theoretically increase…due to temperature dependent increases in fentanyl release and increased skin permeability
4. Life expectancy of less than the length of the primary treatment period (15 days)
5. Subjects whose pain was due to surgery
6. Concomitant treatment with ketoconazole or ritonavir

Study Design: Single-arm, non-randomized, open-label multicenter trial

Study Duration: 15 day primary treatment period with continuation until Duragesic is approved for children or until Duragesic development is stopped

Study conduct:
Opioid tolerant subjects were to be converted from oral/parenteral opioids to Duragesic as follows:

1. The opioid analgesic requirement for the previous 24 hours was to be calculated and converted to the equianalgesic oral morphine dose using the potency conversion table in the current Duragesic label.
2. The oral morphine dose was then to be converted to the appropriate Duragesic dose. A daily intake of 30-44 mg/day of oral morphine was considered appropriate to begin with 12.5 µg/h of Duragesic. A daily intake of 45-134 mg/day of oral morphine was considered appropriate to begin with 25µg/h of Duragesic. Higher doses were to be converted at a ratio of 12.5 µg/h Duragesic for every 45 mg/day of oral morphine.

Duragesic was to be replaced every 72 hours with titration as necessary. Titration was to be based on a conversion of 12.5 µg/h Duragesic for every 45 mg/day of oral morphine equivalent of rescue medication. There was to be a maximum of a 25µg/h increase in Duragesic every 72 hours. Rescue medication usage was to be monitored and recorded for each subject.

Outcome Measures:
Efficacy

- Global assessment-categorical (parent)
- Pain level
  - Vertical visual analog scale (patients 6 years and older)
  - Numeric pain intensity scale (parent/guardian)
  - Scores recorded twice daily by patient and guardian.
  - Additionally, parent/guardian will record pain level at time of rescue use, and one hour later.
- Play performance scale (PPS)
- Child Health Questionnaire
- Rescue medication usage

Pharmacokinetics
Four or five samples per patient for pharmacokinetic analysis

Safety

Vital signs were to be monitored throughout the trial. Respiratory rate and sedation level were to be monitored during the initial 72 hours after application of the Duragesic patch. Bradypnea was defined as a RR < 12 in a 2-6 year old, RR<10 in a 7-10 years old, and RR<8 in a 11 to 16 year old. The combination of bradypnea and excessive sedation were to be recorded as respiratory depression in the CRF. All adverse events were to be tabulated and reported.

Study Results:

Description of patients

The population comprised 199 subjects. The majority were Caucasian (55%) and male (59%). Most of the subjects were preadolescents with a mean age of 10.7 ± 0.28 years. The number of children under 12 years old (48%) was similar to the number of children over 12 years old (41%). Seventy five percent of the subjects were able to start with either a 12.5 µg/h patch (30%) or a 25 µg/h patch (45%).

The subjects had a mean pain duration of 8.3 ±1.3 months, with a median of 1.5 months (range 0.2-120 months). The subjects had a mean baseline pain assessment of 3.7 ±0.3, with a median of 3 (range 0-10 on a numeric pain score scale). All of the pediatric patients had received previous opioid treatment for pain. Seventy percent of the subjects had been taking oral morphine prior to study entry.

Sponsor's summary of Deaths /Discontinuations

The details of deaths and discontinuations, along with further analysis, may be found in the integrated review of safety section.

The majority of the subjects (n=130) completed the initial study phase and entered the extension phase. Twenty-six patients withdrew during the primary treatment phase. Forty-six patients presumably decided not to enter the extension phase, the sponsor has been asked to provide any available reasons for this decision. There were 26 subjects who withdrew during the initial treatment phase. There were 118 subjects who withdrew during the extension phase.

Protocol violations

One hundred forty-five protocol violations occurred during this study, with some pediatric patients having more than one type of violation. One patient was removed from the population due to use of a commercial Duragesic 50 µg/h patch instead of a study patch.

There were eight pediatric patients who did not meet inclusion/exclusion criteria: three were not within the age limits; five did not meet selection criteria NOS. Seven pediatric patients had missing data: seven were missing effectiveness data; three were missing diary data, and three were missing post-baseline data. Eighteen patients had a treatment duration of less than 12 days.

Four pediatric patients had inter-current data violations, representing use of fentanyl or other prohibited medications. There were thirty-one instances of use of other than short-acting opioids.

One hundred twenty seven patients wore their patch over 73 hours, with 22 of them wearing the patch over 84 hours. One hundred nine patients had a treatment interruption of over one hour. Forty-nine patients had a treatment interruption of over 5 hours.

Pharmacokinetics
Pharmacokinetic results will be discussed in Section IV, Pharmacokinetics and Pharmacodynamics.

Efficacy
Efficacy descriptors will be deferred to Section VI of this review, Integrated Review of Efficacy.

Safety
Analysis of safety results will be deferred to the Section VII of this review, Integrated Review of Safety.

FEN-INT-24:
This trial began June 1999 and ended in September 2001.

Title: A fifteen day trial to document the safety, clinical utility and pharmacokinetics of Duragesic (TTS fentanyl) in the treatment of pediatric subjects with continuous pain requiring opioid therapy.

Objective: To determine the safety, clinical utility and pharmacokinetics of 12.5 μg/h Duragesic in the treatment of subjects aged 2-12 with continuous pain requiring the use of a potent opioid

Population: 40 pediatric patients from 2 to 12 years with chronic pain requiring opioids

Key Inclusion Criteria:
1. Patients between 2 and 12 years old, inclusive
2. Chronic pain of a well documented etiology
3. Pain requiring treatment with a strong opioid that is expected to continue for at least 15 days
4. Prior therapy could include a minor analgesic, weak opioid, or strong opioid equianalgesic to 45 mg of morphine or less/day

Key Exclusion Criteria:
1. History of allergy or hypersensitivity to fentanyl or morphine
2. Active skin disease that precludes application of Duragesic or which may affect the application of fentanyl or local tolerability

3. Life expectancy of less than one month
4. Within 3 days of a surgical procedure
5. Concomitant use of protease inhibitors

Study Design: Open-label, non-randomized multi-center trial

Study Duration: 15 days with an extension period of up to one year

Conduct of Study:
All patients were to begin with a 12.5 µg/h Duragesic patch which was then titrated as necessary. Immediate release morphine was to be allowed as rescue medication. Increases in Duragesic were to be based upon previous opioid usage. Titration was to be based on a ratio of 12.5 µg/h Duragesic for up to 45 mg/day of oral morphine rescue and 25 µg/h if the rescue use exceeded 45 mg of oral morphine. Subjects were not to be given any opioid analgesic except for fentanyl and morphine. Five blood samples were to be obtained for pharmacokinetic analysis.

Outcome Measures:
Clinical Endpoints
- 4-point global assessment scale (categorical)
- 4-point treatment assessment (categorical)
- Play performance scale
- Pain level scale (McGrath Faces and McGill VAS)
- Rescue medication use

Safety, rescue medication use and serum fentanyl concentrations were also assessed.

Study Results:
Description of patients
The 53 subjects enrolled on this study were approximately equally distributed between the genders with 28 male subjects and 25 female subjects. The mean age was 6.5 ± 0.5 years. The majority were younger than 6 years old (55%) and had previous opioid exposure (80%). The majority of these pediatric patients (89%, n=50) had malignancies with pain referable to their tumors or their oncologic treatment. The remainder had non-oncologic illnesses: SSPE (1), Olmsted syndrome (1), metachromatic leukodystrophy (1).

Sponsor's summary of Deaths /Discontinuations
The details of deaths and discontinuations, along with further analysis, may be found in the Integrated Review of Safety. Twenty-seven subjects withdrew from this study. The majority of the discontinuations were due to death (n=11), one of these patients died after withdrawing from the study. Other reasons were insufficient response (n=4), adverse events (n=3), ineligibility to continue the trial (n=3), withdrawn consent (n=1) and "other" (n=5).

Protocol violations
Twenty-five protocol violations occurred during this study, with some pediatric patients having more than one type of violation. In three instances eligibility criteria were not met but the pediatric patients were still enrolled in the trial.

Pharmacokinetics
Pharmacokinetic results will be discussed in Section IV, Pharmacokinetics and Pharmacodynamics.

Efficacy
Efficacy descriptors will be deferred to Section VI of this review, Integrated Review of Efficacy.

Safety
Analysis of safety results will be deferred to the Section VII of this review, Integrated Review of Safety.

FEN-GBR-14
This study started in March 1996 and ended in October 1998.

Title: A study to assess the safety, efficacy and pharmacokinetics of Duragesic in the treatment of pediatric patients with chronic pain requiring long-term opioid therapy.

Objective:
- To assess the safety, efficacy and pharmacokinetics of Duragesic in the treatment of pediatric patients with continuous pain requiring long-term opioid therapy
- To provide health care professionals with experience of using Duragesic in the treatment of chronic pain requiring long-term opioid therapy

Population: At least 38 pediatric patients with chronic pain requiring opioids

Key Inclusion Criteria:
1. Patients with a confirmed malignancy or other life threatening/terminal disease requiring treatment with a strong opioid
2. Expected to continue to require use of a strong opioid through the course of the study, terminal patients with a life expectancy less than fifteen days were still permitted to enroll
3. Received a stable dose of IR oral morphine or SR morphine for at least 48 hours immediately prior to trial entry. For patients on SR, one or two additional doses of IR morphine did not exclude participation. The minimum daily dose of morphine for entry was to be 30 mg.

Key Exclusion criteria:
1. Allergy or hypersensitivity to morphine
2. Active skin disease precluding use of Duragesic

Study Design: Open-label, non-randomized multi-center trial

Study Duration: 15 days with an extension period of up to one year

Conduct of Study:
Treatment Phase

- Subjects were to be converted from oral/parenteral opioids to Duragesic.
- The minimum starting dose was to be 25 μg/h.
- Duragesic was to be replaced every 72 hours with titration as necessary. Titration was to be done in 25μg/h increments. Rescue medication usage was to be monitored and recorded for each subject.
- The maximum recommended dose was to be 300 μg/h.
- IR morphine was to be provided as rescue medication

Extension Phase

- Indefinite duration
- Efficacy and safety data collected every 2 weeks for the first three months
- Subsequent collection of AE, rescue/concomitant medication use, Duragesic use was to be collected "on an ongoing basis."

Outcome Measures:
Efficacy

- Patient treatment assessment
- Investigator/parent global assessments
- Play performance scale (PPS)
- Disease progression scale
- Rescue medication usage
- Constipation/diarrhea record
- Pain level
  McGrath faces
  Investigator assessment of pain

Safety
All adverse events were to be tabulated and reported.

Pharmacokinetics
A total of 13 blood samples were to be obtained per subject.

Study Results:
Description of patients
The population comprised 41 subjects. The majority were male (73%). Most of the subjects were preadolescents with a median age of 10.5 years. The majority (88%, n=36) had malignancies. The remainder had neurological illnesses: Sanfilippo's syndrome (1), Friedreich's ataxia (1), Duchenne's muscular dystrophy (2) and cerebral palsy/static encephalopathy (1).

Sponsor's summary of Deaths /Discontinuations
The details of deaths and discontinuations, along with further analysis, may be found in the Integrated Review of Safety.

Fifteen subjects discontinued during the treatment phase. Eight were reported to discontinue due to an adverse event. Four had insufficient response and three withdrew consent.

Nineteen withdrew during the extension phase. Nine withdrew due to an adverse event. Two each withdrew due to insufficient response or cessation of symptoms. Three withdrew consent and three withdrew for other reasons.

Protocol violations
Two protocol violations occurred during this study. These pediatric patients received Duragesic despite not having met the minimum dose specified for trial entry, 30 mg/day of morphine. There was no entry dose stated for patient 8. Patient 25 was on a dose of 5 mg of morphine before starting the study.

Efficacy
Efficacy is deferred to Section VI of this review, Integrated Review of Efficacy.

Safety
Analysis of safety results will be deferred to Section VII of this review, Integrated Review of Safety.

FEN-FRA-4
This study was performed from March 1990 through April 1991, prior to the 1995 black box warning contraindicating the use of Duragesic for postoperative analgesia.

Title: Protocol for pharmacokinetic study of transdermally administered fentanyl in young children

Objective: To study the different pharmacokinetic parameters of transdermally delivered fentanyl for postoperative analgesia in young children without hepatic or renal pathology

Population: Eight pediatric patients. Eight adults aged 30-65 years, undergoing similar types of surgery, were used as controls. These adults were recruited from three French hospital centers.

Inclusion Criteria (only provided for the pediatric patients):
Age 1-5 years and scheduled to undergo a major surgical operation of $\geq$ three hours

Exclusion Criteria (only provided for the pediatric patients):
1. Weight less than 10 kilos

2. Major deficiency of the respiratory, cardiac, hepatic , renal or central nervous system
3. Intolerance to morphine or fentanyl
4. Opiate dependency
5. Peri-operative blood loss more than or equal to 10% of estimated blood volume

Study Design:
Open-label, multi-center, single-arm, single-dose nonrandomized pharmacokinetic study using adult controls

Study Duration: 144 hours

Conduct of Study:
Duragesic was to be applied to the thoraces of the pediatric patients 2 hours prior to induction of anesthesia.

Postoperatively the patients were to be monitored in a PACU before being transferred to the PICU. While in the PACU, IV morphine could be administered as rescue medication. While in the PICU, SQ morphine could be administered as rescue medication.

Blood for fentanyl levels were to be drawn at the time of patch application, and at 4, 6, 8, 12 hours. The sampling was to be done every 12 hours while the patch was still applied. Samples were to be taken at 4, 6, 12, 24, 36, 48, 60, and 72 hours after the patch was removed.

Study Results:
Deaths /Discontinuations
There were no study discontinuations. There was one study death, an adult with arrhythmia and coagulation disorder. No narrative was prepared for this patient as per the sponsor.

Adverse events
Two of the eight adult subjects had at least one adverse event, as did three of the eight pediatric subjects.

The adverse events reported for the adults were arrhythmia, coagulation disorder and disorientation.

The adverse events reported for the pediatric subjects were respiratory distress, sedation, somnolence and urinary retention.

Pharmacokinetic results
The results of this single dose pharmacokinetic study are discussed in Section IV, Human Pharmacokinetics and Pharmacodynamics.

B. Tables Listing the Clinical Trials

Table 1:
Table listing clinical trials with gender and age information

Trial	Gender		Age in years				
	M	F	<2	2<6	6-12	12<16	16-18
FEN-FRA-4	*	*	1	7	0	0	0
FEN-GBR-14	30	11	0	11	12	11	7
FEN-INT-24	28	25	1	27	21	4	0
FEN-USA-87	118	81	1	27	67	102	2
Total	176	117	3	72	100	117	9

*-data not provided

C. Postmarketing Experience

Duragesic is marketed in adults for the treatment of chronic pain requiring opioid analgesia. It is currently approved in 64 countries and marketed in 57 countries (volume 231.2, p.6). It has not been withdrawn in any country due to safety or efficacy concerns.

The original safety database included 510 adult patients (357 acute use/153 chronic use, with over half of the latter using the medication for more than 30 days). The adverse events included nausea, vomiting, constipation, somnolence, and diaphoresis. Respiratory depression was seen in fewer than 5 % of patients: 4% of acute postoperative users and 2% of the chronic users. The current Duragesic label notes the following adverse reactions that were reported post-marketing: edema, tachycardia, weight loss, blurred vision.

FEN-FRA-4 was performed from March 1990 through April 1991, prior to the 1995 black box warning contraindicating the use of Duragesic for postoperative analgesia.

The sponsor searched it's internal pharmacovigilence database for post-marketing reports of AEs in pediatric patients under 16 years old (see appendix A). While a third of the reports were expected adverse events that are included in the adverse reaction section of the Duragesic label, there were other events that were unexpected. For example, there were two instances of inadvertent transfer of the patch from a patient to a child, one of whom died. In addition, there were six instances of abuse: four oral ingestions; two topical applications. The AERS database has fewer than ten reports of Duragesic misuse or abuse in pediatric patients under 16.

D. Literature Review

The sponsor has presented a summarized review of the literature on fentanyl in the pediatric population from January 1 1964 through May 9 2002.

The sponsor cites four pediatric studies in support of the pharmacokinetic data: an abstract; articles based on the findings from FEN-FRA-4 and FEN-GBR-14; a small pilot study done at the [redacted]. Supportive pharmacokinetic studies done in adults were provided as well as articles on the pharmacology of fentanyl (volume 231.7). Multiple studies were cited reporting Duragesic use in pediatric patients.

Two publications have been produced based on the results of the submitted studies.

1. Paut O, Cambouilves J, Viard L, Lemoing JP, Levron JC. Pharmacokinetics of transdermal fentanyl in the perioperative period in young pediatric patients. Anaesthesia 2000; 55: 1192-1212(based on FRA-4)
2. Hunt A, Goldman A, Devine T, Phillips M. Transdermal fentanyl for pain relief in a pediatric palliative care population. Palliative Medicine 2001; 15:405-412 (based on GBR-14)

This reviewer used the following additional references:
Ahmedzai S, Brooks D. et al. Transdermal fentanyl versus sustained release oral morphine in cancer pain: preference, efficacy and quality of life. J of Pain and Symptom management 1997; 13 (5): 254-261)

Noyes M, Irving H. The use of transdermal fentanyl in pediatric palliative care. American journal of hospice and palliative care 2001; 18 (6): 411-16

Collins JJ, Dunkel IJ et al. Trandermal fentanyl in pediatric patients with cancer pain: feasibility, tolerability and pharmacokinetic correlates. Journal of Pediatrics 1999; 134: 319-23

IV. Human Pharmacokinetics and Pharmacodynamics

A. Pharmacokinetics

Fentanyl is a synthetic opioid agonist that interacts primarily with μ-receptors distributed in the brain and spinal cord as well as other tissues. Clinically the principal effects are referable to the central nervous system, where it produces analgesia, sedation and/or drowsiness. While major cardiovascular effects are not usually seen, orthostatic hypotension and syncope have been reported. The effects on urinary smooth muscle are variable with complaints of urinary frequency and urgency both having been reported.

Studies with adults have demonstrated that after an initial gradual increase in fentanyl concentration, peak concentrations occur between 24 and 72 hours after initial application of Duragesic. The concentration of fentanyl measurable in the serum increases over the first few Duragesic applications. After approximately 5 applications, a steady-state serum concentration is reached.

In adults, fentanyl is noted to accumulate in skeletal muscle and fat from which it is released slowly into the blood. Importantly, there is an apparent skin depot effect associated with use of the transdermal fentanyl system. The range of elimination half-life upon cessation of Duragesic use is 13-22 hours as compared to the 3-12 hour half-life range after administration of intravenous fentanyl.

The primary metabolic pathway for fentanyl is the human cytochrome P450 3A4 isoenzyme system. Fentanyl is metabolized through oxidative N-dealkylation to inactive metabolites. Studies done after intravenous administration of fentanyl show predominantly renal excretion of metabolites with less than 10% of the original dose found in fecal matter.

The sponsor derived the information on pharmacokinetics and pharmacodynamics in the pediatric population from study FEN-FRA-4 as well as pooled population pharmacokinetic data from studies FEN-INT-24 and FEN-USA-87, which was used for the pharmacokinetic modeling. FEN-GBR-14 did not provide enough pharmacokinetic samples to allow evaluation.

FEN-FRA-4

Pharmacokinetic analyses

The Duragesic dose in the pediatric patients was 2.5 times that of the adults based on a calculation of µg/kg/h.

As demonstrated in Table 2, the maximal plasma fentanyl concentration (C_{max}) was 54% higher in the pediatric population.

While the time to maximal concentration (T_{max}) was shorter in the pediatric subjects, there was also a wider range of values.

The study report suggested that the cutaneous depot effect may be less evident in the pediatric population.

Table 2:
Fentanyl pharmacokinetic parameters (mean and SD)

	Dose	C_{max} (ng/ml)	T_{max} (h)	AUC_{0-144h} (ng.n/ml)	C_{ss} (ng/ml)	$t_{1/2}$
Children	25 µg/h	1.7 ± 0.66	18 ± 11	87 ± 28	*	14.5 ± 6.2
Adults	50 µg/h	1.1 ± 0.51	33 ± 5	71 ± 28	0.75 ± 0.3	20.6 ± 5.7

* This value was not given since it was only obtained for 2 of the 8 patients.
(volume 231.5/54)

Results from population pharmacokinetics (PPK) analysis (INT-24 and USA-87):

A total of 886 evaluable serum samples, representing 73% of the maximal expected number, were obtained from 242 pediatric patients: 50 subjects from FEN-INT-24 and 192 subjects from FEN-USA-87. Forty of the youngest patients were able to provide

evaluable samples. The only pharmacokinetic data provided by these studies were clearance and steady state concentration. No information on volume of distribution, Cmax, t_{max}, $T_{1/2}$ or AUC could be determined from these studies due to the sparse population pharmacokinetic sampling methods used.

The patient population, presented in Table 3, is not identical to that of the ISS since there are ten fewer patients in the PPK analysis. Ethnicity information was not collected in FEN-INT-24.

Table 3:
Demographics for pediatric patients in pooled pharmacokinetic analysis

	Statistics	All subjects	<6 yrs	6 to <12 yrs	>12 yrs
Wt (kg)	n	241	52	86	103
	Mean ± SD	35 ±19	16 ± 4	29 ± 10	50 ± 19
	Median (range)	31(11-139)	15 (11-26)	27 (14-65)	47 (20-139)
Ht (cm)	n	235	51	86	103
	Mean ± SD	134 ±24	101 ±11	29 ±10	50 ±19
	Median (range)	137 (76-180)	103 (76-123)	27(14-65)	47(20-139)
BSA (m^2)	n	242	52	87	103
	Mean ± SD	1.12 ±0.39	0.67 ±0.1	1.02 ±0.21	1.44 ±0.31
	Median (range)	1.08(0.5-2.4)	0.66(0.5-0.9)	1 (0.6-1.6)	1.45 (0.8-2.4)
Sex	Male	141	28	57	56
	Female	100	24	29	47
Race	White	147	35	53	59
	Hispanic	44	7	16	21
	Black	41	6	13	22
	Asian	3	2	1	0
	Other	6	2	3	1
Race	White	147	35	53	59
	Hispanic	44	7	16	21
	Black	41	6	13	22
	Asian	3	2	1	0
	Other	6	2	3	1

(Table reproduced from volume 231.5/138, where the sponsor notes that the demographic data for one patient was missing at the time of database transfer for PK analysis)

A statistical model was derived with these covariates:

- Study # and site
- Patient demographics (age, gender, race)
- Patient physical characteristics (weight, height, body surface area (BSA), body mass index (BMI), lean body mass (LBM), body temperature, Tanner stage)
- System administration related variables (Time from dosing, system location, dosing gap)
- Concomitant medications (cytochrome P-450 3A4 (CYP3A4) inhibitor or a CYP3A4 inducer)

There was no correlation between fentanyl steady state concentration and adverse events such as nausea, vomiting, fever. In addition, there was no correlation between fentanyl steady state concentration and patient age, gender, race, or Tanner stage for sexual maturity. Alterations in body temperature, location of system application and administration of concomitant medications also had no effect on fentanyl concentrations. The analysis of concomitant medications specifically looked for the effects of CYP3A4 inhibitors including cimetidine, erythromycin, fluconazole, metronidazole as well as the effects of CYP3A4 inducers such as phenobarbital, dexamethasone and phenytoin and found no effect. This may be due to the small number of subjects on these products, given the known effects of CYP3A4 inhibitors in adults.

The sponsor noted that some pharmacokinetic samples were obtained shortly after the first system was applied and others were obtained following a dosing gap, defined as more than one hour between patch removal and patch replacement or the wearing of a given patch for over 72 hours. When these samples were excluded, expected steady state conditions were confirmed.

Both steady state concentration (see Table 4) and drug clearance were dependent on body surface area, study site and time from dosing. The sponsor reports that "an increase in BSA of 0.1 m^2 is predicted to result in a 4.8% increase in clearance and a 4.6% decrease in steady-state concentration. (Volume 231.2, page 10) " The presence of age related differences in clearance in the pediatric population has been evaluated by the Biopharmaceutics reviewer. Refer to the Biopharmaceutics review for further details..

Table 4:
Clearance data from population pharmacokinetics model

	Pediatric data	Adult data
Clearance estimate (CE)	28.1 ±15.32 L/h	28.1 ± 15.32 L/h
CE adjusted for body weight	0.92 ±0.51 L/h/kg	0.77 ± 0.3 L/h/kg
CE adjusted for body surface area	26 ±13 L/h/m^2	19 ± 7 L/h/m^2

After analyzing the data, the sponsor concluded that serum concentrations are not as useful as subjective responses in guiding therapy. The study site effect was thought to be a possible reflection of "demographic differences between the study sites". Due to the large number of sites with a small number of enrolled subjects, demographic difference as a covariate within sites was not evaluated. The sponsor postulates that the study site effect on serum concentrations might be due to "demographic differences between the sites." If the sponsor is aware of or believes that there is a potential for demographic differences in the absorption of fentanyl, this should be studied further. Those further studies would not have to necessarily be done in the pediatric population.

B. Pharmacodynamics

Discussion of pharmacodynamics has been incorporated into the efficacy section of this review.

V. Clinical Review Methods

A. How the Review was Conducted

Volumes 231.1-44 were reviewed in whole or in part, along with the case report tables (CRTs) and Case report forms (CRFs) that were provided as electronic files. The material reviewed for safety in the pediatric population comes from the studies submitted in this supplement as well as the 120-day safety updates provided.

The study protocols, study reports and study results were reviewed for FEN-USA-87 and the other three 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. In addition, data points from a random sample of adverse events were followed through the appendices, CRTs and CRFs.

The sponsor's information on financial disclosure was reviewed.

The AERS database was reviewed for reports of Duragesic related adverse events.

B. Overview of Materials Consulted in Review

The 56 paper volumes submitted in support of this application were reviewed as were the electronic CRF and CRT files.

C. Overview of Methods Used to Evaluate Data Quality and Integrity

A DSI audit was not requested by the Division.

D. Were Trials Conducted in Accordance with Accepted Ethical Standards

The trials were conducted in accordance with accepted ethical standards.

E. Evaluation of Financial Disclosure

The sponsor has provided financial information from the investigators who participated in FEN-USA-87 and FEN-INT-24, the two studies conducted after implementation of the regulations outlined in 21 CFR Part 54.

The Sponsor was contacted to determine whether there was any record of payments for investigators who did not return financial disclosure forms. The sponsor confirms that no payments were made to the subinvestigators. The sponsor reports having performed due diligence to obtain the missing forms.

FEN-USA-87

The sponsor has submitted financial disclosure form 3455 for the [redacted] This form was submitted to disclose a significant payment of greater than $25,000 from the trial sponsor to [redacted] for her work as an overall [redacted] and her site enrolled 5 (3%) patients into FEN-USA-87.

The sponsor has submitted financial disclosure form 3455 for the [redacted] This form was submitted to disclose a significant equity interest of greater than $50,000 worth of Johnson & Johnson stock held in trust for her children. [redacted] and her site enrolled 2 (1%) patients into FEN-USA-87.

The sponsor has submitted financial disclosure form 3455 for [redacted] enrolled no patients into FEN-USA-87.

Seven of the sub-investigators for FEN-USA-87 did not complete financial disclosure forms (PI's name, # subjects enrolled at the site):

[redacted]) subjects enrolled)

[redacted], 0 subjects enrolled)

[redacted] 2 subjects enrolled)

[redacted] ubject enrolled)

[redacted] ubjects enrolled)

The sponsor submitted certification with a form 3454 for the remainder of the FEN-USA-87 Principal Investigators and their sub-investigators.

FEN-INT-24

The sponsor submitted certification with a form 3454 for the FEN-INT-24 Principal Investigators and their sub-investigators. Although the clinical investigators had "not entered into any identifiable, disclosable financial arrangements with Johnson & Johnson or any of its affiliates" according to the provided form 3454, many of the investigators were missing financial disclosure forms at study initiation, at study closure and/or at one year post study follow-up.

Summary

The financial disclosure information for FEN-USA-87 appears adequate based on a review of the provided information. Although one investigator was being paid as a [redacted] the number of patients enrolled by [redacted] (n=5, 3%) is too small to influence the study outcome. The financial disclosure information for FEN-INT-24 is incomplete since only 56% (n=9) of the principal investigators ever provided financial disclosure forms. The financial disclosure status of multiple sub-investigators for this study is also incomplete.

The Sponsor was contacted to determine whether there was any record of payments for investigators who did not return financial disclosure forms. The sponsor confirms that no

payments were made to the subinvestigators. The sponsor reports having performed due diligence to obtain the missing forms.

VI. Integrated Review of Efficacy

A. Brief Statement of Conclusions

These studies were open-label, uncontrolled pharmacokinetic and safety studies. Efficacy measures were used to guide titration and use of rescue medication.

Overall pain intensity scores improved to a small degree over the study period. The global assessments of efficacy were improved from baseline.

Play performance scale ratings (PPS) were improved overall and were positively correlated with better parental and investigator assessments of patch efficacy, side effect profile and convenience. These outcomes, along with the absence of a significant increase in rescue medication usage, suggest that Duragesic provided a measure of analgesia.

In the absence of an appropriately controlled double-blind study, no definitive comments can be made about drug efficacy.

B. General Approach to Review of the Efficacy of the Drug

The protocols for studies FEN-USA-87 FEN-INT-24, and FEN-GBR-14 have been discussed in section III so only study related efficacy descriptions will be given here.

C. Detailed Review of Trials by Indication

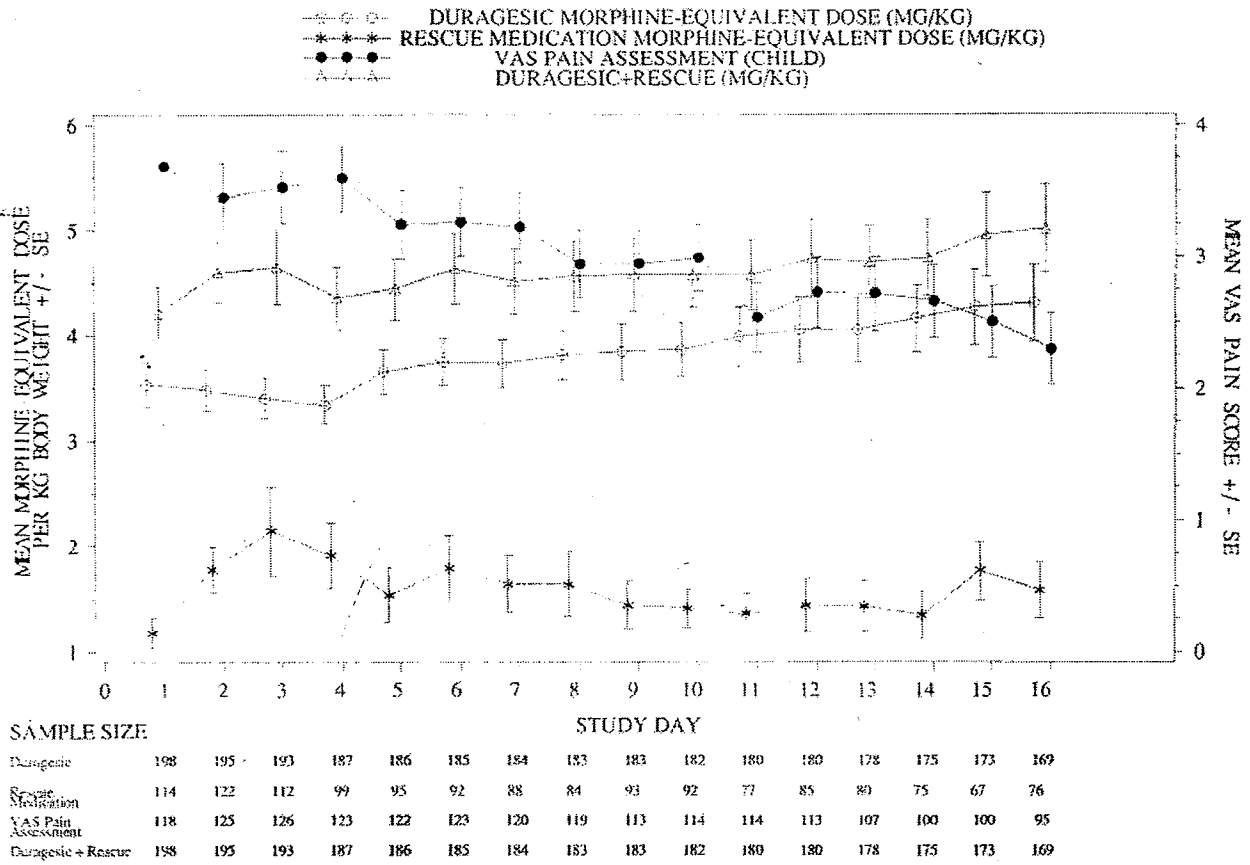
FEN-USA-87

Rescue Medication Use

The combined use of Duragesic and rescue was associated with decreased pain intensity according to parental and child reports of VAS scores (see Graph EFF 10 reproduced from sponsor's submission). While the pain intensity plots presented below, based on the data from the primary treatment period of USA-87, cannot be superimposed, the VAS scores are trending downward in both cases. There is noted to be increased use of rescue medication in the first three days, which may reflect the effect of conversion from oral/parenteral treatment to a transdermal formulation. There is also an increase in rescue medication use on day 15, but that may be an artifactual increase based on the decreased sample size.

The use of rescue medication will be further discussed in section VIII, Dosing Regimen and Administration.

GRAPH EFF.10 PAIN REDUCTION IN RELATION TO DURAGESIC AND RESCUE MEDICATION DOSE FOR THE PRIMARY TREATMENT PERIOD--CHILD ASSESSMENT
POPULATION: INTENT-TO-TREAT



SAMPLE SIZE																
Duragesic	198	195	193	187	186	185	184	183	183	182	180	180	178	175	173	169
Rescue Medication	114	122	112	99	95	92	88	84	93	92	77	85	80	75	67	76
VAS Pain Assessment	118	125	126	123	122	123	120	119	113	114	114	113	107	100	100	95
Duragesic + Rescue	198	195	193	187	186	185	184	183	183	182	180	180	178	175	173	169

Pain level-Parent/Guardian

Of the 199 patients enrolled, 162 were assessed at baseline and 174 were assessed at the endpoint, defined as the last non missing post-baseline observation through the last day of study medication in the primary treatment period.

When the summaries of parental reported average daily pain intensity were assessed, the change from baseline was less than 2 points on a 10 point scale in all measures. The mean pain intensity for the male patients decreased from 3.4±0.3 to 2.4±0.3, with a decrease in the median from 2.9 to 1.4. The mean pain intensity for the female patients decreased from 3.7±0.4 to 3±0.4, with a decrease in the median from 3.9 to 2 (range 0-9.9).

Pain level-Child (age 6-12 years)

Of the 199 patients enrolled, 118 were assessed at baseline and 133 were assessed at the endpoint, defined as the last non missing post-baseline observation through the last day of study medication in the primary treatment period.

When the summaries of patient reported pain intensity were assessed, the change from baseline was less than 1 point on a 10 point scale in all measures. The mean pain intensity for the male patients decreased from 3.5±0.3 to 3.1±0.3. The mean pain intensity for the female patients decreased from 4±0.4 to 3.1±0.5.

Global Assessment

Of the 199 patients enrolled, 189 were assessed at baseline and 149 were assessed at the endpoint, defined as the last non missing post-baseline observation through the last day of study medication in the primary treatment period.

Overall global assessments of pain revealed that the majority of subjects rated their pain treatment as good (34.9%) or fair (30.7%) when measured at baseline. At the treatment endpoint, the majority assessed their treatment as good (34.9%) or very good (52.3%). The proportion of patients rating treatment as good or very good was similar across the evaluated age ranges. While at baseline a smaller percentage of female patients rated their pain control as good when compared to male patients (26.3 % vs. 40.7 %), by the end of the study, the percentages were closer (male patients 33.3% vs. female patients 37.1%).

When baseline assessment was compared with endpoint assessment, 4 pediatric patients (all male) who had originally rated their pain treatment as very good/good lowered their ratings to fair/poor after 15 days of treatment with Duragesic. Fifty-four pediatric patients who initially rated their pain treatment as fair/poor improved their ratings to very good/good at the end of the primary treatment period. The majority of the worsened perceptions of pain treatment took place in the pediatric patients under 12 years old. The improved perception of pain treatment was fairly evenly split between pediatric patients under and over 12.

Play Performance Scale (PPS)

A play performance scale (Table 5) was used to evaluate the subjects' level of daily functioning.

Of the 199 patients enrolled, 180 were assessed at baseline and 171 were assessed at the endpoint, defined as the last non missing post-baseline observation through the last day of study medication in the primary treatment period.

At the end of the primary treatment period, the parents of 75 subjects rated the patch as very good; these subjects had a mean PPS score of 61.5±3. The subjects whose parents rated the patch as poor had a mean PPS score of 12.5±3.

The pediatric patients with a higher average daily Duragesic dose (morphine equivalents >4 μg/h/kg) had consistently lower PPS scores than pediatric patients who had a lower Duragesic requirement (morphine equivalents 0-4 μg/h/kg). However, the mean and median PPS scores showed improvement from Day 1 of therapy in all groups (see Table 6).

Table 5:
Play performance scale

Normal range of play 100-fully active, normal 90-minor restrictions in physically strenuous play/activity 80-active but tires more easily
Mild to moderate restriction of play 70-both greater restrictions of, and less time spent in activities/active play 60-up and around, but minimal active play, keeps busy with quieter activities 50-gets dressed but lies around most of the day; no active play; able to participate in quiet play
Moderate to severe restriction of play 40-mostly in bed, participates in quiet activities 30-in bed; needs assistance even for quiet play 20-oftern sleeping, play entirely limited to very passive activities 10-no play, does not get out of bed 00-unresponsive

Table 6:
PPS scores divided by morphine equivalent dose/day

Morphine equivalents (# of subjects)	Mean PPS score	Median PPS score
Day 1		
0-2 µg/h/kg (61)	44.92 ± 3.05	50
2-4 µg/h/kg (70)	41.71 ± 2.8	40
>4 µg/h/kg (48)	35.42 ± 2.73	40
Day 16		
0-2 µg/h/kg (43)	61.86 ± 3.28	60
2-4 µg/h/kg (41)	61.46 ± 4.02	60
>4 µg/h/kg (48)	51.25 ± 3.47	50

(231.13/59)

When PPS scores were evaluated in the setting of the decision to continue or discontinue the study, the pediatric patients who completed the study began with a mean PPS score of 43±1.8 and ended with a PPS score of 55±2. Those pediatric patients who did not complete the initial treatment period had worse PPS score at baseline, 29±4, with an average last recorded PPS score of 35±5. The mean final score reflected an improvement but it was still lower than the baseline score for the pediatric patients who did complete the treatment period.

Child Health Questionnaire (CHQ)

This questionnaire was completed by patients aged 10 to 16. The parent questionnaire was used in patients aged 5-16. The CHQ uses a four week recall period so it was collected once at baseline and then monthly during the extension phase.

There are no comparative values for patients who withdrew during the primary treatment period, declined participation in the extension phase, or did not complete the questionnaire.

At the end of the first month, parents reported improvement compared to baseline in the following domains: mental health, family activity, physical, emotional behavior and physical role. On average, patients reported improvement in bodily pain, physical role and physical functioning.

FEN-INT-24

Rescue medication use

The use of rescue medication will be further discussed in section VIII, dosing, regimen and administration. Overall the amount of rescue was fairly constant through the trial.

Pain intensity assessed by the investigator

The assessment of pain intensity was limited to the primary treatment period. Of the 53 patients enrolled, 53 assessments were available at baseline and at the endpoint, defined as the last non missing post-baseline observation through the last day of study medication in the primary treatment period.

The majority of the patients had pain described by the investigator as moderate (40%) or severe (32%) at baseline. At the endpoint, the majority had no pain (57%) or mild pain (14%) perceived by the investigator.

Pain intensity scale (McGrath Faces)

The collection of pain level scale information was limited to the primary treatment period. Of the 53 patients enrolled, 47 baseline assessments were available and 51 assessments were available at the endpoint, defined as the last non missing post-baseline observation through the last day of study medication in the primary treatment period.

The mean baseline score was 2.3 with a standard error of 0.2. At the endpoint, the mean score was 1.3 with a standard error of 0.3. There were no differences by age or gender.

Pain intensity scale (McGill VAS)

The collection of pain level scale information was limited to the primary treatment period. Of the 53 patients enrolled, 47 baseline assessments were available and 49 assessments were available at the endpoint, defined as the last non missing post-baseline observation through the last day of study medication in the primary treatment period.

The mean baseline score was 38.2 with a standard error of 4.02. At the endpoint, the mean score was 25.4 with a standard error of 4.53. While there were baseline differences by age and gender, there were no differences at the endpoint.

Global assessment of pain control

The global assessment of pain control was limited to the primary treatment period. Of the 53 patients enrolled, 41 parental assessments were available and 45 investigator assessments were available at the endpoint, defined as the last non missing post-baseline observation through the last day of study medication in the primary treatment period.

The majority of the investigator's assessments were excellent (42%) or good (31%) with 9% rated as poor. The parental assessments were similar with 44% rating pain control as excellent, 32% rating it as good and 12% each rating pain control as fair or poor.

Treatment assessment

The treatment assessment was limited to the primary treatment period. Of the 53 patients enrolled, 46 were assessed at baseline and 47 were assessed at the endpoint, defined as the last non missing post-baseline observation through the last day of study medication in the primary treatment period.

The majority rated their pain treatment as fair (41%) or poor (24%) at baseline. At the end of the primary treatment period, the majority rated their pain as good (47%) or very good (30%). The majority of the subjects whose pain had originally been rated as poor/fair at baseline improved their assessment to good/very good by the endpoint (64%). One subject whose baseline assessment had been good/very good worsened his rating to poor/fair.

Play performance scale (see Table 5)

The play performance scale ratings in study INT-24 ranged from 59/100 to 68/100 at the final assessment. The average change from baseline was 44 points. There were no significant differences in the ratings when analyses by age and by gender were performed.

When the play performance scores were evaluated by the level of treatment satisfaction, there was a marked difference between the group who rated the patch as unsuccessful and the group which rated the patch as successful. The former group had a Day 16 mean play performance score of 22.5 (a decrease of 14 points from baseline), while the latter group had a Day 16 mean play performance score of 69.6 (an increase of 28 points from baseline).

As would be expected, when the PPS score was evaluated in the context of the daily average pain scores, patients with less pain had higher PPS scores. However, all pediatric patients had increased PPS scores on Day 16. The pediatric patients with the most pain, i.e. those with VAS >50-100, had a mean score of 43.3 (a 9.2 point change from baseline). The pediatric patients with mild-moderate pain, i.e. those with VAS 10-50, had a mean score of 48.6 (an 8.1 point change from baseline). The pediatric patients with no pain had a mean score of 77.5 (a 21.5 point change from baseline).

A review of PPS score by patch dose revealed that PPS score in pediatric patients receiving the 12.5 µg/h patch was consistently higher throughout the trial than the PPS score in pediatric patients receiving patches in any of the higher strengths. This may reflect the effect of worse pain and/or disease progression in pediatric patients requiring more than 12.5 µg/h for pain control.

FEN-GBR-14

Rescue medication usage

The use of rescue medication will be further discussed in section VIII, dosing, regimen and administration. Overall the amount of rescue was fairly constant through the trial.

Patient treatment assessment

Of the 41 patients enrolled, 25 assessments were available on Day 3 (the first day recorded) and on Day 15.

At the initial assessment, the majority of parents rated the patch as good (49%) or very good (17%). At the Day 15 assessment, the majority of the parents still rated the patch as good (56%) or very good (28%).

Play performance scale (PPS)

The median PPS score started at 50 and remained at 50 through the trial.

Pain intensity (McGrath faces)

The letter pain scores were converted to a numerical score with 0 being the best and 1 being the worst. A score of 0.59 (category E) or below was considered an acceptable pain level. A score above 0.59 was unacceptable. The ratings were done twice daily. On day 0, eleven subjects had one unacceptable pain rating and seven had two unacceptable pain ratings. On Day 15, four had one unacceptable pain level and one had two unacceptable pain levels.

Investigator/parent global assessments

The majority of the investigators (67.5%) had the impression that the treatment was good or very good by day 15. The majority of the parents agreed, with 70% rating the treatment as good or very good.

Disease progression scale

The majority of the subjects (68%) showed deterioration over the study period.

Constipation/diarrhea record

Seventeen subjects noted loose bowels on day 0, only eight noted this on day 15. Eight complained of constipation on day 0, three had this complaint on day 15.

D. Efficacy Conclusions

These studies were all open-label investigations so they cannot provide evidence of drug efficacy.

Pain intensity as determined by parents or guardian showed a change of less than 20%. The pain intensity levels as measured by the patients changed less than 10%.

The majority of patients, physicians and parents/guardians gave the treatment a global assessment rating of good or very good/excellent.

There was a clear positive correlation between higher play performance scores and treatment satisfaction. Children with low play performance scores had higher pain intensity ratings and lower global assessments.

VII. Integrated Review of Safety

A. Brief Statement of Conclusions

Duragesic may be used safely in the pediatric population. The adverse events seen in the pediatric trials mirrored the adverse events documented for the adult population.

There were 94 deaths during these trials. There was no clear correlation between use of study drug and death in any of these patients, many of whom (97%) had underlying malignancies.

Serious adverse events (SAE) occurred in over half (57%) of the participants in these trials, with neoplasm being the most commonly reported.

The common adverse events during these trials were nausea, vomiting, constipation, somnolence, and diaphoresis, comparable with the adverse events seen in the adult patient population using Duragesic. The incidence of these adverse events remained steady over the primary and extension periods.

The majority of the patients were taking at least one other medication while on study-99.5%. The use of fentanyl in conjunction with CNS sedatives, antiemetic therapy, and/or chemotherapy was associated with a higher incidence of adverse events.

The emergence of opiate withdrawal symptoms on conversion from morphine to fentanyl has been reported in adults. Few pediatric patients reported withdrawal symptoms during the trials. It should be noted that these symptoms may occur in conjunction with adequate pain control.

B. Description of Patient Exposure

Demographics

The Integrated Summary of Safety (ISS) database, comprising 293 patients, represented results from three studies: FEN-USA-87, FEN-INT-24 and FEN-GBR-14. The majority of the pediatric patients (see Table 7) who participated in these studies were male (n=176, 60.1 %), Caucasian, (n=156, 61.9%) and lived outside of the United States of America (n=177, 60.4%).

Table 7:
Demographics for the ISS

	Statistics	All subjects
Age in years	n Mean Median (range)	293 9.7 10 (1-18)
Ht (cm)	n Mean Median (range)	280 133.8 137 (69-181)
Wt (kg)	n Mean Median (range)	290 34.9 31 (7-139)
Sex	Male Female	176 117
Race	White Hispanic Black Asian Other	156 45 41 4 6

Most of the pediatric patients were in the first decade of life, with a mean age of 9.7 years. Two one-year-old pediatric patients were enrolled in violation of the protocol inclusion criteria. One was erroneously included in the youngest age group (2-6 year olds), the other was not included in the analyses by age category since she was under 2 years old. Nine patients were ≥16 years old from study FEN-GBR-14. Of the 241 pediatric patients for whom Tanner staging was assessed, most were preadolescent i.e. Tanner stage 1 (54.5% of females, 61.3% of males).

The majority of the pediatric patients (74%) had pain related to an underlying malignancy or its treatment (see appendix B). All patients with pain related to oncologic treatment, such as chemotherapy related mucositis were reclassified by this Reviewer as having pain due to malignancy. Pediatric patients with pancreatitis (4%) and pediatric patients with sickle cell disease (4%) represented the next largest groups of patients. A detailed list of the diagnoses for the trial participants is given in appendix B.

Over 70% of the pediatric patients had nociceptive pain (n=189, 71.4%), with the remainder having either neuropathic (n=36, 14%) or multiple pain types (n=35, 14%). The duration of pain ranged from one day to ten years in the combined population from studies FEN-INT-24 and FEN-USA-87, with a mean of 6.8 months (volume 231.2, p.16). The pediatric patients in study INT-24 had a mean of 1.3 months (±0.42) of continuous pain.

Subject disposition

A total of 301 pediatric patients were treated with Duragesic. All three studies began with a fifteen day study treatment phase followed by an extension phase. With the exception of the oldest patients, >75% of patients in each age group completed the trial (see Table 8).

Table 8:
Pediatric patients who completed the primary treatment period by age and study group

Age in years	<2	2<6	6<12	12<16	16-18
FEN-GBR-14	0	7 (64%)*	7(58%)	9 (82%)	3 (43%)
FEN-INT-24	1 (100%)	17 (63%)	15 (71%)	3 (75%)	0
FEN-USA-87	0	25 (93%	55 (82%)	92 (90%)	1 (50%)
All	100%	75%	77%	89%	44%

*The percentages given are the percentage of patients in a given age group.

While 80% (n=235) of the population completed the primary treatment period, only 58% (n=171) of the population entered the extension phase. The majority of the patients in these studies had fewer than sixty days of Duragesic exposure (see Table 9).
As of the ISS cutoff date of November 25 2002, 12 patients on FEN-USA-87 were receiving ongoing Duragesic treatment.

Table 9:
Duragesic exposure by time interval

Time Interval	Original ISS n(%)	120 day update n(%)
Total number of subjects	293	293
0-72 hours	15 (5.1)	15 (5.1)
>72 hours-15 days	44 (15)	44 (15)
16-30 days	136 (46.4)	125 (42.7)
31-60 days	48 (16.4)	47 (16.0)
61-90 days	11 (3.8)	11 (3.8)
91-120 days	14 (4.8)	13 (4.4)
121-270 days	16 (5.5)	20 (6.8)
>270 days	9 (3.1)	18 (6.1)

(table reproduced from ISS safety update 234.1/75)

The sponsor was asked to provide the reasons for failure to enter extension phase. The sponsor responded that the decision to enter the extension phase was a matter of individual discretion. The CRFs did not capture reasons for the decision not to continue.

There were 58 withdrawals during the primary study treatment period, a detailed list is provided in Appendix C. The investigators in study FEN-GBR-14 classified death as an adverse event. Deaths have been separated out by this Reviewer to form a discrete category in Table 10 so the deaths reported in GBR-14 have been reclassified. The majority of the withdrawals in the primary treatment period were due to death (n=22). The next largest group was patients complaining of insufficient response (n=15). One patient withdrew consent because he did not want to stay in the hospital. One child was withdrawn from the study due to impending discharge from the hospital. This last case was originally classified under category other, and was moved to ineligible to continue trial.

There were 139 withdrawals during the extension treatment period, a detailed list is provided in Appendix C. The deaths reported in GBR-14 have been reclassified as previously stated. Two patients who left the country were originally classified as other but were reclassified as ineligible to continue the trial. Sixteen patients complained of insufficient response, this category includes patients who had to change to another analgesic for better pain management, and those who needed more frequent patch changes then allowed by the protocol. Seven patients had consent withdrawn for reasons such as wishing greater flexibility in patch management or " tired of collecting data."

Table 10: Subject disposition

	Disposition	USA-87	INT-24	GBR-14
Began treatment	293	199	53	41
Completed 15 day study treatment period	235 (80%)	173	36	26
Withdrawals during study treatment period	58 (20%)	26	17	15
Death	22 (38%)[a]	6	8	8
Adverse event other than death	8 (14%)[a]	6	2	0
Withdrew consent	4 (7%)[a]	1	1	2
Insufficient response	13 (22%)[a]	5	3	5
Decreased need for opiate	5 (9%)[a]	2	3	0
Patient noncompliance	2 (3%)[a]	2	0	0
Ineligible to continue trial	3 (5%)[a]	3	0	0
Other	1 (<1%)[a]	1	0	0
Did not enter extension treatment period	64 (27%)[b]	43	18	3

Table 10: Subject disposition (continued)

	Disposition	USA-87	INT-24	GBR-14
Entered extension treatment period	171(58%)	130	18	23
Discontinued**	139(81%)[a]	104	15	20
Death	42 (30%)[a]	26	6	10
Adverse Event	13 (9%)[a]	12	1	0
Withdrawal of consent	13 (9%)[a]	10	0	3
Insufficient response	23 (17%)[a]	17	2	4
Decreased need for opiate	24 (17%)[a]	21	1	2
Patient noncompliance	2 (1%)[a]	1	0	1
Ineligible to continue trial	19 (14%)[a]	15	4	0
Using commercial Duragesic	12 (9%)[a]	11	1	0
Other	5 (4%)[a]	5	0	0
Completed (GBR-14, INT-24)	6	0	3	3
Ongoing (USA-87)	12	12	0	0

(data derived from volumes 231.2, 231.8, 231.29, 231.31, ISS update) *Three additional pediatric patients in FEN-GBR-14 did not receive Duragesic despite entering the extension treatment period

[a] The percentages represent the percentage of patients who withdrew for a given reason

[b] The percentage represents the percent of patients eligible to continue who chose not to do so

C. Methods and Specific Findings of Safety Review

Summary

In addition to the ISS, the Sponsor provided a table with safety data from the pharmacokinetic study FEN-FRA-4, which was done prior to the black box warning contraindicating use of Duragesic in the management of postoperative pain. The black box warning was added because of the occurrence of two deaths when Duragesic was used in opioid-naïve postoperative patients.

Two of the eight adult subjects, in Study FEN-FRA-4 had at least one adverse event, as did three of the eight pediatric subjects. The adverse events reported for the adults were arrhythmia, coagulation disorder and disorientation. The adult subject with the first two adverse events died. The adverse events reported for the pediatric patients were respiratory distress, sedation, somnolence and urinary retention.

The ISS includes pooled results from studies FEN-USA-87, FEN-INT-24 and FEN-GBR-14, for a total of 293 patients. FEN-INT-24 and FEN-GBR-14 were completed at the time of initial submission so that submission included complete safety data from the primary treatment period as well as the extension period. For FEN-USA-87, all data accumulated from the primary treatment period are included as well as data from persons who entered and ended the extension period on or before 3 March 2002. The data for persons ongoing in study FEN-USA-87 are complete through 25 November 2002. As previously discussed

the safety data from FEN-FRA-4, a single dose pharmacokinetic study, were not integrated into the ISS.

The majority of subjects (91%) had adverse events reported. Nausea and vomiting were the most common specific adverse events during both periods, other than non-treatment emergent neoplasm. Overall incidence of AEs was higher during the primary study treatment period than during the extension period.

Deaths

The ISS and 120-day safety update report 94 deaths, tabulated in Appendix D. The death of subject A30064 (FEN-USA-87), a six year old with metastatic neuroblastoma, was recorded as an SAE and coded as doubtfully related to treatment by the investigator. The other 93 deaths were all coded as not related to treatment. The majority of deaths (n=87, 92.6%) occurred during treatment or within thirty days of treatment cessation. Seven deaths occurred more than thirty days after treatment. The sponsor notes that five deaths in study FEN-GBR-14 were not included in the database since they occurred more than thirty days after cessation of therapy and were considered unrelated to treatment.

The majority of the deaths in the primary treatment phase and the extension phase were due to progression of underlying malignancies. There were three cases, summarized below, with a possible correlation to use of study medication. In all three instances, the primary investigator did not feel that there was a correlation between study drug and the involved subject's demise. A review of the narratives and case report forms did not suggest a correlation between death and use of the study medication but the information provided was insufficient to make a definitive determination..

- GBR-14/029: A 16 year old ([redacted] with a past medical history significant for dysphagia, aspiration and dyspnea. Within [redacted] day of beginning study medication, he had an episode of emesis with aspiration, and subsequent cyanosis. He died that day. While fentanyl induced nausea/vomiting could have played a role in his demise, his known history of prior aspiration episodes makes it unclear what role, if any, study drug played in his death.
- GBR-14/069: A 17 year old (relapsed acute lymphoblastic leukemia) who had just completed a five day course of chemotherapy. [redacted] after placement of the study medication, he vomited and subsequently had a cardiac arrest. While fentanyl induced vomiting with subsequent aspiration could have played a role in his death, the history of recent chemotherapy administration might have made him more likely to experience episodes of nausea/vomiting. While it is possible that study drug contributed to his demise, it is improbable given the short duration of study drug exposure.
- INT-24/A30096: A 3 year old (sub-sclerosing panencephalitis) was described as experiencing encephalopathic changes, peripheral edema and agitation on [redacted] of therapy. On the day of her death, [redacted] her medication was increased from 200µg/h to 300µg/h. While it is possible that the increase in study drug contributed to her demise, it is improbable given the short duration of exposure to the increased dosage.

Of the deaths that occurred in patients off study, the majority were due to progression of underlying malignancies. Most occurred more than 4 days after the last use of study medication, which would allow for the passage of five drug half-lives. There were four cases that occurred within four days of the last use of the study medication. In all instances the primary investigator did not feel that there was a correlation between study drug and the involved subject's demise. A review of the narratives and case report forms failed to provide evidence of a causal relationship between the patient's death and use of study drug.

- USA-87/A30065: A 9 year old (osteosarcoma) who withdrew from the trial due to severe pain after 28 days of therapy. He died — after withdrawing from the trial.
- GBR-14/33: A 12 year old (glioma) who withdrew from the trial due to severe pain after 21 days of therapy. He died while receiving diamorphine infusions, — after withdrawing from the trial.
- GBR-14/44: A 4 year old (rhabdomyosarcoma) who withdrew from the trial due to severe pain after 21 days of therapy. He died while receiving diamorphine and midazolam infusions, — s after withdrawing from the trial.
- GBR-14/105: A 6 year old (neuroblastoma) who withdrew from the trial due to uncontrolled pain after 14 days of therapy. He died while receiving diamorphine, levomepromazine and midazolam infusions, — after withdrawing from the trial.

Serious Adverse Events (SAE)

Over half of the subjects (n=166, 57%) in the population of 293 patients had at least one SAE, with neoplasm being the most common (see table 11, a complete list of SAE is presented in Appendix E). Neoplasm was reported as an SAE in 46% of the pediatric patients but did not represent a new event for any of these patients. Fever, granulocytopenia, and pain were the most common serious adverse events, which is not unexpected in this population of children with malignancies.

Table 11:
Incidence of specific SAE occurring in >5% of subjects

Number with at least one SAE	166 (57%)
Neoplasm	77 (46%)
Fever	31 (19%)
Granulocytopenia	15 (9%)
Pain	14 (8%)
Vomiting	11 (7%)
Dyspnea	9 (5%)
Respiratory Insufficiency	9 (5%)
Thrombocytopenia	8 (5%)
Sepsis	8 (5%)
Anemia	8 (5%)

Modification of table ISS update AE.13AB. The percentages given are the percentage of the 166 patients who experienced at least one SAE.

Neoplasm (46%), fever (19%), granulocytopenia (9%), pain (8%), vomiting (7%) respiratory insufficiency (5%), and dyspnea (5%) were all reported as SAE during these trials. These adverse events can be associated with malignancy and other terminal illnesses.

While no cases of neoplasm resolved after stopping Duragesic, in many cases (see subsection entitled deaths) patients had worsening of their underlying malignancies while on therapy. Further details about patients' responses to adverse events may be found in the subsection entitled adverse events of special concern.

Discontinuations due to adverse events

A total of 197 patients withdrew during the treatment period, as shown in Table 10. The majority of discontinuations were due to death (n=64, 32%). Discontinuations for reasons other than death or adverse event are tabulated in Appendix C. Twenty-one patients withdrew due to adverse events, as shown in Table 12 below.

There were 5 patients who withdrew due to adverse events definitely related to use of study drug. These adverse events included application site reaction, somnolence/sedation, fatigue/slurred speech/mental slowness, obstipation and pain/anxiety with patch removal.

There were 4 patients who withdrew due to adverse events possibly related to use of study drug. These adverse events included lactic acidosis/altered mentation, agitation, fever/nausea/vomiting/headache, and pruritis/skin abrasions.

The other patients withdrew for reasons that were unrelated to use of study drug, insofar as can be determined from review of case report forms.

Table 12:
Patients who withdrew due to adverse events

Study / Patient #	Age/sex	Adverse event (s)	Study day	Dose
USA-87 A30020	15/F	Application site reaction	28	0.21 µg/kg/h
USA-87 A30025	12/F	Bone marrow transplant	24	2.64 µg/kg/h
USA-87 A30079	14/M	Somnolence/sedation	12	0.19 µg/kg/h
USA-87 A30088	15M	Irritability/Nervousness	63	0.42 µg/kg/h
USA-87 A30094	15/F	Loss of appetite	74	1.19 µg/kg/h
USA-87 A30110	2/F	Abdominal pain, mucositis	56	0.83 µg/kg/h
USA-87 A30186	3/F	Lactic acidosis, Altered Mentation	26	0.83µg/kg/h

Table 12:
Patients who withdrew due to adverse events

Study / Patient #	Age/sex	Adverse event (s)	Study day	Dose
USA-87 A30203	15/F	Agitation	2	0.88 µg/kg/h
USA-87 A30321	15/M	Pulmonary edema	13	0.56 µg/kg/h
USA-87 A30335	10/F	Typhilitis	27	0.78 µg/kg/h
USA-87 A30367	13/F	Erythema gangrenosum	17	0.81 µg/kg/h
USA-87 A30389	15/M	Pruritis/Skin abrasions	9	0.52 µg/kg/h
USA-87 A30396	13/F	Renal insufficiency	19	1.02 µg/kg/h
USA-87 A30406	15/M	Fever/Nausea/Vomiting/Headache	13	0.64 µg/kg/h
USA-87 A30504	14/F	Focal seizure	30	0.31µg/kg/h
USA-87 A30536	12/F	Cerebral hemorrhage/fever/loss of consciousness/tremor/vomiting	3	0.96 µg/kg/h
USA-87 A30535	6/M	Loss of consciousness/ Cerebral hemorrhage	32	2.78 µg/kg/h
INT-24 A30004	4/F	Pain/anxiety with patch removal	22	11.77 µg/kg/h
INT-24 A30076	5/F	Fatigue/Slurred speech/mental slowness	3	1.09 µg/kg/h
INT-24 A30086	5/F	Obstipation *opioid naïve patient*	9	0.78µg/kg/h
GBR-14 058	2/M	Night awakening/ Insufficient resp	7	2.17 µg/kg/h

Adverse events

While 90% of subjects reported at least one AE during treatment, fever and/or vomiting were reported by approximately one third of patients. The incidence of AE reported by >2% of subjects in either the primary or extension treatment period is displayed in Appendix F.

Neoplasms and hematological disorders were reported as adverse events, in this population of pediatric patients with pre-existing solid and hematological malignancies. Since the neoplasms and hematological disorders did not represent treatment-emergent events it is difficult to assess what casual role, if any, Duragesic had. Additionally hospitalizations for chemotherapy were reported as adverse events. Since the pediatric

patients had known malignancies, it is improbable that Duragesic played a role in these scheduled hospitalizations.

The investigators considered the following to be related to trial medication: nausea and vomiting, diaphoresis, confusion, agitation, constipation, pruritis, somnolence, headache, and application-site reaction. With the exception of application site reactions, these adverse events are all expected complications of malignancies and terminal diseases in children. In light of this fact, it is not possible to apportion causality of these adverse events to use of study drug versus underlying disease.

There was no trend towards increase or decrease in adverse events over time when duration of Duragesic exposure was assessed. The number of affected individuals with a given AE of any severity, by duration of exposure, is shown in Table 13.

Table 13: Incidence of AE occurring in >5% of subjects by duration of exposure

	Duragesic								
	Duration of exposure								
	Total n=293	0-72 hours n=293	>72 hours-15 days n=278	16-30 days n=234	31-60 days n=109	61-90 days n=62	91-120 days n=51	121-270 days n=38	>270 days n=18
# of affected subjects	268	163	220	119	77	37	30	31	12
Vomiting	98	39	45	21	13	5	2	2	1
Nausea	69	19	38	12	8	2	4	2	0
Abdominal Pain	43	8	26	7	5	2	2	0	1
Constipation	38	7	19	5	5	3	1	4	2
Diarrhea	37	6	17	7	4	3	1	0	0
Fever	103	35	46	21	13	3	1	6	0
Pain	39	5	20	7	8	0	1	2	1
Edema	18	4	9	2	4	2	0	0	0
Dyspnea	17	0	11	3	0	1	1	1	1
Headache	47	9	23	7	5	3	1	5	1
Pruritis	39	13	22	5	3	1	0	1	0
Rash	20	4	12	2	1	0	0	0	1
Somnolence	21	8	9	2	3	0	0	0	1
Insomnia	20	3	8	2	5	2	0	1	1
Infection	19	2	5	6	4	1	2	2	1
Neoplasm	69	11	17	14	16	4	7	11	1
Thrombocytopenia	34	10	18	8	6	1	1	1	0
Site Reactions	19	3	11	2	4	0	0	0	0

Modification of sponsor's table AE.06B(The numbers given are the number of affected individuals)

Appendix F displays the incidence of AE, of any severity, occurring in >2% of subjects in either primary or treatment phase. The AEs that occurred in under 2% of subjects are tabulated in Appendices G and H. There was no clear association of AE with Tanner

sexual maturity rating. There was no correlation between patch placement and adverse events. Patches were applied to the upper arm, chest, upper and lower back, abdomen, and leg among other areas. However, in a few pediatric patients (n=19) who wore the patch on their leg, only 52% experienced an adverse event as opposed to the 70-75% of subjects who experienced adverse events while wearing the patch elsewhere on their bodies.

Vital signs

The vital signs were not collected uniformly across the three studies. Blood pressure was not collected in studies FEN-INT-24 or FEN-GBR-14. Temperature was not collected in study FEN-GBR-14.

Clinical significance was defined as a change of at least 25% from baseline (see Table 14a). The majority of the patients had changes in respirations (71%). Over half (59%) had a significant change in pulse. These changes could reflect effect of study drug on the cardiovascular system or its analgesic effect. It is not possible to determine which is the case with the information that was provided for review. The mean changes all changed by one unit of measurement or less (see Table 14b).

Table 14a: Vital signs: Subjects with a 25% change from baseline

	Number of subjects ≥25%	Percent ≥25%	Number of subjects ≤25%	Percent ≤25%
Pulse (beats/min)	96	32.8	78	26.6
Systolic Blood Pressure (mmHg)	37	12.6	27	9.2
Diastolic Blood Pressure (mmHg)	76	25.9	60	20.5
Respirations (breaths/min)	122	41.6	86	29.4

Reproduction of table 10:10 from sponsor's ISS update

Table 14 b: Mean changes from baseline

Parameter	Temperature (°C)	Pulse (BPM)	SBP (mmHg)	DBP (mmHg)	RR (Resp/min)
Studies where collected	INT-24/USA-87	All	USA-87only	USA-87only	All
End of Week 1	0.05 (217)	0.8 (242)	-0.7 (174)	-1.0 (174)	0.2 (246)
End of Primary treatment period	0.05 (195)	0.5 (211)	-0.8 (164)	-1.0 (164)	-0.2 (209)

Note: the number in parentheses represents the number of subjects evaluated (231.38/284)

D. Adverse Events of Special Concern

Adverse events of special concern by age group are displayed in Appendix I. The only noteworthy finding is that the sponsor reported two adolescents with withdrawal symptoms. This reviewer found a wider age range of children with withdrawal symptoms as will be discussed below.

Oral exposure

Due to the known propensity of pediatric patients to put things into their mouths, it was recommended that the patch be placed on the upper back area of the youngest pediatric patients when possible. There were no reports of oral ingestion of the patch by participants in these clinical trials.

Opioid Withdrawal

As these trials attempted to determine the optimal method of dose titration in a predominantly opiate tolerant/dependant population, the possibility of opiate withdrawal during the conversion from oral or parenteral opiates to a transdermal system was a serious concern.

The sponsor reported two pediatric patients with withdrawal syndrome that occurred during treatment (summarized below). Narcotic withdrawal was also reported in subject A 30039 on Day 26 but her last dose of trial medication was on Day 16.

- A 15 year old (pancreatitis, A30418) had withdrawal symptoms deemed nonserious and possibly related to Duragesic. The episode, which lasted 16 days, occurred when the child had been on 25 µg/h (0.34 µg /kg/hr) of Duragesic for 67 days. There was no disruption of Duragesic treatment and the subject was reported to have recovered.
- A 14-year old (pancreatic cancer, GBR-025) had withdrawal symptoms that were deemed nonserious and definitely related to Duragesic. The episode, which was characterized by pain, restlessness and diaphoresis, lasted 1 day. It occurred when the child had been on 150 µg/h (4.77 µg /kg/hr) of Duragesic for 8 days. He had removed the patch before the episode but 5 hours later he "agreed to have it replaced." The replaced system was also 150µg/h but was increased to 175µg/h at the next system application.

In addition to the pediatric patients reported above, on review of the adverse event reports, three other pediatric patients (summarized below) had symptoms consistent with opiate withdrawal on initial patch conversion, although they were not coded as such by the investigators.

- A 15 year old girl (ALL, A30203) had severe agitation along with nausea and diaphoresis on Day 2 of Duragesic treatment with 75µg/h (0.88 µg /k/h).). She had previously been on 96 mg of IV morphine/day, although in the 24 hours prior to starting the study she was given 288 mg morphine. All three events were considered very likely related to Duragesic treatment by the investigator. This subject withdrew from the study as a result of these adverse events. She recovered from this SAE once study drug was discontinued.

- A 15 year old boy (nasopharnygeal carcinoma, A30104) had severe insomnia and moderate diaphoresis on Day 1 of Duragesic dosing with treatment with 37.5µg/h (0.99 µg /k/h). He had previously been on 180 mg of morphine/day. Both events were considered probably related to Duragesic treatment by the investigator. No intervention was made. He continued on the study medication until Day 91, when it was discontinued due to a SAE, eccymosis.
- A 3 year old boy (metastatic neuroblastoma, GBR-020) had insomnia, vivid dreams, agitation and confusion on Day 3 of Duragesic dosing with treatment with 25µg/h (1.47 µg /k/h). No rescue medication was given nor were other interventions made. He recovered from these AE and continued on study drug until his death on study Day 24.

In the published article based on study FEN-GBR-14, the investigators reported that symptoms consistent with withdrawal, e.g. diaphoresis, diarrhea, abdominal discomfort, stuffy nose and depression were detected in three pediatric patients upon conversion from oral opioids to transdermal patch. The investigators for that study noted that where recognized the symptoms responded to rescue doses of opioid or spontaneously resolved within 3 days (231.32/380). The patients referenced above, GBR-025 and GBR-020, may have been two of those patients but that cannot be definitively ascertained from the narratives and case report forms provided.

The sponsor was contacted in an attempt to determine the study ID numbers for the three patients that the FEN-GBR-14 investigators thought might have had withdrawal. The sponsor's response was "the statements made in the publication were interpretations made by the authors at the time of preparation of the manuscript and were not recorded as cases of withdrawal during the study. Listed below are those patients in our database whose constellation of reported AEs matches that discussed as representing possible withdrawal: patients GBR-1, GBR-13, and GBR-16 (fax from sponsor 4/21/2003)."

- A 15 year old (neuroblastoma, GBR-1), being treated with 50µg/h Duragesic (1.47 µg /k/h), had diaphoresis and increased hunger on Day 1. On Day 2, she complained of "feeling weepy" but had no complains of pain. On Day 3, she noted diaphoresis and depression. She received 10 mg of oramorph on study day 3. By Day 5, she was feeling better according to her diaries. She continued on study drug until her death on
- A 3 year old (metastatic Wilms tumor, GBR-13), being treated with 25µg/h Duragesic (1.6 µg /k/h), had " a blocked nose" on Days 0 and 1 but no complaints of pain until Day 2. She received 2 doses of 6 mg of oramorph on study Days 1 and 2. She discontinued study drug on Day 3. By Day 5, she was feeling better according to her diaries.
- A 15 year old (Ewings sarcoma, GBR-16), being treated with 50µg/h Duragesic (1.36 µg /k/h), had " abdominal pain" on Days 0-5. She received 12 mg of Oramorph on study Days 0-3. On Day 1, she received an additional 8 mg of Oramorph. She recovered from her AE. She was discontinued from the trial once

she ran out of diary forms without notifying the investigator, on Day 45. However, she continued to use commercially available Duragesic.

Opioid toxicity

Respiratory Insufficiency

While respiratory depression is a known serious risk of Duragesic use, in this group of patients with terminal disease, in the majority of cases it is not clear that there is a correlation between study drug use and the adverse event of respiratory insufficiency.

- A 14 year old (ALL) had bradypnea described as a SAE beginning on day 23, within 3 days of end of therapy. On the same day, this subject was reported to have dyspnea, decreased responsiveness and cardiac failure. Death occurred on study — While use of study drug may have been a factor in his respiratory symptoms, it seems more likely that he had reached the terminal phase of his illness.
- A 5 year old boy (A30093, metastastic neuroblastoma) using a 25 µg/h patch (1.563 µg /kg/hr) died on — of therapy. On the same day, this subject was reported to have gastrointestinal bleeding, thrombocytopenia, leukocytosis, cardiac and terminal respiratory arrest. While use of study drug may have been a factor in his respiratory symptoms, it seems more likely that he had reached the terminal phase of his illness.
- An 11 year old girl (A30313, renal cancer metastatic to lung) using a 12.5µg/h patch (0.625 µg /kg/hr) — of disease progression. On the same day, this subject was reported to have cardiac failure and respiratory insufficiency. While use of study drug may have been a factor in her respiratory symptoms, it seem more likely that her symptoms reflected her lung metastases.
- An 11 year old (ALL, A30097) using a 75µg/h patch (1.36 µg/kg/hr) died on study — of disease progression. While use of study drug may have been a factor in his respiratory symptoms, it seems more likely that he had reached the terminal phase of his illness.
- An 11 year old male (A30531, diabetes insipidus, bladder pain) had his 12.5µg/h Duragesic patch (0.28 µg /kg/hr) temporarily removed on day 1 with subsequent recovery from AE after 2 days. His respirations went from 20/min at baseline to 13 on Day 3. With temporary cessation of the 12.5 µg/h patch, the SAE resolved. Treatment was resumed at the same dose. On Day 16, his respiratory rate was noted to be 14/min. No intervention was made at that time. His respiratory rate went from the higher end of normal at 20 breaths/minute to low normal at 13 breaths/minute, which may reflect Duragesic effect on respiration or on pain.
- A 15 year old (JRA, A30548) had respiratory insufficiency reported on 1.72µg/h, 22 days on therapy, 16 days on dose. No action was taken for this SAE, which was ongoing. She was noted to have concurrent fungal pneumonia, which was the probable reason for her respiratory difficulties.

- A 10 year old male (A30530, brain abcesses) had his Duragesic patch, 12.5µg/h, temporarily removed with subsequent recovery from AE after 4 days. This AE was probably correlated with Duragesic therapy though it did not recur with continued Duragesic use.

Agitation/Nervousness

Three pediatric patients had a dose change made due to agitation/nervousness. All three recovered from this AE after the dose change was made.

- An 18 year old (Ewing's sarcoma) had a dose reduction to 25 µg/h after having been on 100 µg/h for 4 days.
- A 15 year old (ALL) had Duragesic permanently stopped after having been on 75 µg/h for 2 days.
- A 15 year old (Neuropathic pain following hip subluxation surgery) had Duragesic permanently stopped after having been on 12.5 µg/h for 63 days.

Somnolence

Seventeen of the 23 reports of somnolence occurred in the first 15 days of treatment. The majority of the patients experiencing this AE recovered without intervention. Five pediatric patients, summarized below, had a dose change made due to somnolence with subsequent recovery from this AE.

- An 18 year old (Ewing's sarcoma) had a dose reduction to 50 µg/h after having been on 75 µg/h for 21 days.
- A 6 year old (A30026, neuroblastoma) had a dose reduction to 25 µg/h after having been on 37.5 µg/h for 12 days.
- A 14 year old (metastatic osteosarcoma) had Duragesic permanently stopped after having been on 12.5 µg/h for 12 days.
- A 14 year old (A30200, sickle cell disease) had a dose reduction to 200 µg/h after having been on 225 µg/h for 2 days.
- A 14 year old (A30079) who was receiving 12.5 µg/h (0.19µg/kg/hr) withdrew from the study due to this AE. He recovered after study drug was removed.

Vomiting

Most of the patients who experienced vomiting resolved without intervention. A 6-year-old (metastatic neuroblastoma) receiving 12.5µg/h was reported not to have recovered but he still completed the primary treatment phase and entered the extension period. Four pediatric patients, summarized below, had dose changes made due to vomiting.

- A 9 year old (osteosarcoma) had a dose reduction from 25 µg/h to 12.5µg/h with subsequent recovery from AE.
- A 16 year old (PNET) had his Duragesic patches, which initially totalled 550 µg/h, lowered to 300 µg/h then stopped. He withdrew from the study two days after the onset of the AE due to insufficient pain control and died subsequent to last contact.

- A 12 year old (A30536, ANLL) who experienced vomiting beginning on Day 2 in conjunction with cerebral hemorrhage, fever, loss of consciousness had her Duragesic patches stopped on Day 3, with subsequent cessation of vomiting though the other AE were unresolved. While there is a possible correlation between the study drug and her vomiting, there is no clear correlation with her other symptoms.
- A 15 year old (A30406, ALL) experienced multiple episodes of vomiting. He recovered from the first with no intervention. His treatment with Duragesic was stopped at the third episode, on Day 13. He recovered from this AE after stopping study drug so there was a probable correlation between this AE and use of study drug.

Nausea

While the majority of the pediatric patients had no change in Duragesic in response to this AE, five pediatric patients had dose changes made due to nausea.

- A 15 year old (A30094, nonmalignant chronic pain for 4 years) had her Duragesic patch, 37.5µg/h, removed with subsequent recovery from the AE.
- A 15 year old (A30406, leukemia), with concurrent AE of fever and headache, had his Duragesic patch, 25µg/h removed without subsequent recovery from AE.
- A 16 year old (PNET) had his Duragesic patches stopped. (This patient is discussed in the vomiting subsection.)
- A 15 year old (A30419, chronic pancreatitis) had a dose reduction from 50 µg/h to 12.5 µg/h with subsequent recovery from the AE.
- A 13 year old (A30455, chronic pancreatitis) had a dose reduction from 37.5 µg/h to 25 µg/h with subsequent recovery from the AE.

E. Summary of Critical Safety Findings and Limitations of Data

These trials demonstrated that that it is possible to make a safe transition from oral/parenteral administration of opiate to a transdermal formulation in an opioid-tolerant pediatric population.

There were 97 deaths in the population of 293 patients. While almost a third of the participants died, this is not unexpected in a population of pediatric patients with predominantly solid malignancies.

Neoplasm, which did not represent a treatment emergent event, was the most commonly reported SAE. Fever and pain were also commonly reported. These SAE are not unexpected in the population under study.

The overall incidence of AEs was higher among males than females (94% versus 86%). The incidence of fever, anemia and thrombocytopenia decreased with age

of the subjects, which may reflect the underlying diagnoses. Headache and abdominal pain were more common in the eldest pediatric patients, those over 12 years old. Prepubertal subjects (Tanner stage 1) patients had a higher incidence of somnolence. Pubertal subjects (Tanner 2-5) had a greater incidence of insomnia. The youngest pediatric patients, those under 6 years old, had the highest incidence of AE reported at 98.5%. It may or may not be relevant that these pediatric patients were also receiving the highest per kilo doses of Duragesic during these trials.

Upon evaluation by underlying cause of pain, Tanner scales and initial Duragesic dose, no clinically relevant differences were noted in overall adverse event incidence. There were no unexpected adverse effects. The serious and non-serious adverse effects seen in this trial reflected the adverse events seen in the original trials of Duragesic in adults with malignancies.

There were no problems specifically attributable to Duragesic except application site reactions. The incidence of this complaint declined over time but it is not clear whether that is due to patients becoming used to the patch or whether it is due to patients deciding not to continue the study.

Fever, diarrhea, abdominal pain and nausea were all more common among US subjects and among Caucasians. While Black subjects had an AE incidence of approximately 80%, all other ethnic groups had an AE incidence of greater than 90%.

The percentage of opioid naïve pediatric patients (n=8, enrolled in study INT-24) with a non-oncologic AE was equal to or less than the percentage of opioid tolerant pediatric patients with a given non-oncologic AE.

Although only two pediatric patients were specifically stated to have withdrawal syndrome, review of the data shows that at least 8 (3%) pediatric patients had symptoms consistent with opioid withdrawal.

VIII. Dosing, Regimen, and Administration Issues

Results from pooled studies

Initial Dose

Safe and effective conversion from oral/parenteral opiates to Duragesic therapy was assessed using a population of 293 patients (see Table 15). The majority of the pediatric patients (97.3%, n=285) in these studies were opioid tolerant on enrollment, less than 3% (n=8) were opioid naïve upon study entry. Most pediatric patients were initiated with either 12.5 µg/h (n=111, 38%) or 25 µg/h (n=123, 42%) of Duragesic.

The patients on USA-87 were converted to Duragesic based on their previous morphine requirement. Patients who were receiving less than the equivalent of 45mg morphine began with 12.5µg/h Duragesic. Pediatric patients who began with 25µg/h Duragesic had been receiving the equivalent of 45-134mg morphine daily. All patients on FEN-GBR-14 were to begin with 25µg/h Duragesic or more based on their previous morphine requirement. All patients on FEN-INT-24 were to begin with 12.5µg/h.

Table 15:
Dosing and titration (pooled studies)

	Statistic	Treatment period		
		Primary	Extension	Overall
Number of subjects	n	293	168	293
Dose of analgesic taken before starting Duragesic (mg/kg/day)[1,2]	n Mean (SE)	276 3.3 (0.21)	164 3.2 (0.28)	P[6]
Duration of treatment with Duragesic (days)	n Mean (SE)	293 14.4 (0.23)	168 88.1 (11.23)	293 64.9 (6.96)
Time until first titration warranted (days)	n Mean (SE)	121 5.6 (0.24)	58 45.7 (16.06)	151 24.0 (7.38)
Time until subsequent titrations warranted[3]	n Mean (SE)	55 3.82 (0.22)	38 20.93 (3.54)	94 11.83 (1.50)
Dose of Duragesic (µg/kg/h)				
Overall	n Mean (SE)	290 1.19 (0.06)	167 1.91 (0.2)	290 1.47 (0.1)
Initial Dose	n Mean (SE)	290 0.96 (0.04)	167 1.56 (0.15)	P[6]
Final dose[4]	n Mean (SE)	290 1.4 (0.09)	167 2.47 (0.32)	290 2.00(0.2)
Dose of total opioid[1,5] (mg/kg/day)				
Overall	n Mean (SE)	290 4.89 (0.26)	167 7.44 (0.74)	290 5.81 (0.37)
Initial dose	n Mean (SE)	290 3.95 (0.185)	167 6.14 (0.56)	P[6]
Final dose[4]	n Mean (SE)	290 5.6 (0.36)	167 9.32 (1.19)	290 7. 6 (0.73)
Ratio of Duragesic to total opioid				
Overall	n Mean (SE)	293 0.91 (0.01)	168 0.94 (0.01)	293 0.92 (0.01)
Initial dose	n Mean (SE)	293 0.90 (0.01)	168 0.95 (0.01)	P[6]
Final dose[4]	n Mean (SE)	293 0.93 (0.01)	168 0.96 (0.01)	293 0.96 (0.01)

[1]Reported as its oral ME
[2]Computed for subjects who had a dose greater than 0 within 24 hours of starting Duragesic

[3]Relative to the day of the first titration in that period
[4]Defined as the last dose greater than 0 during that period
[5]Represents the sum of the total Duragesic dose plus rescue medications (FEN-USA-87 and the primary treatment period of FEN-INT-24) or only the total daily Duragesic dose (FEN-GBR-14 and the extension treatment period of FEN-INT-24)
P=identical to primary period
(ISS update Table 7:2)

Duration of therapy

The mean duration of Duragesic therapy was 65 days. In the primary treatment period, 41% (n=121) of the participants required dose titration with a mean of 5.6 days until the first dose titration was warranted. Of the 121 patients who received their first dose titration during the initial treatment period, 55 (45%) required subsequent dose titration with an average time to subsequent titration of 3.8 days. As previously discussed in the Integrated Review of Safety, there were instances of temporary or permanent cessation of Duragesic usage due to SAE. There were no instances where patients who resumed Duragesic therapy resumed on dose that was lower than their initial dose.

Dose during extension period

Similar to the primary treatment period, most pediatric patients entered the extension period (n=168) receiving 12.5 µg/h (n=60, 36%) or 25 µg/h (n=72, 43%) of Duragesic. The 168 patients who entered the extension period had a mean Duragesic therapy duration of 88 days. In the extension period, 39% (n=66) of the participants required dose titration with a mean of 46 days until the first dose titration was warranted. Of the 66 patients who received dose titration during the extension period, 38 (58%) required subsequent dose titration with an average time to subsequent titration of 21 days.

Rescue medication

Duragesic represented 90% or more of the total opioid daily requirement for the subjects, with the remainder representing rescue medication used for breakthrough pain (see table 16). Rescue medication was used at least once by 89% of the subjects. The mean oral dose of rescue medication was inversely correlated with body weight. The mean oral dose of rescue medication was lowest in the subjects using the lowest strength patch at baseline and the mean dose of oral rescue was higher in persons with malignancies than in those with pain of non-malignant origin. The majority of the pediatric patients used morphine or hydromorphone as rescue medication. Fifteen pediatric patients used fentanyl, which was allowed during surgical procedures. Nine of the fifteen received a single dose of fentanyl as concomitant therapy. Five pediatric patients received 3 to 12 doses of fentanyl as rescue. One patient received 73 doses of fentanyl as rescue. Although these fifteen patients were reported as protocol violations, only one, who received a single dose, was excluded from the pharmacokinetic database.

Table 16: Rescue medication use (pooled studies)

Rescue medication	Primary treatment period n=252 (86% of 293)	Extension period n=88 (68% of 130)
Morphine	212 (84%)[a]	63 (72%)
Hydromorphone	34 (13%)	17 (19%)
Oxycodone	17 (7%)	9 (10%)
Fentanyl	15 (6%)	5 (6%)
Codeine	14 (6%)	1 (1%)
Tramadol	12 (5%)	8 (9%)
Meperidine	11 (4%)	6 (7%)
Hydrocodone	5 (2%)	3 (4%)
Methadone	5 (2%)	5 (6%)

[a]The percentages for each medication represents the percentage of rescue using pediatric patients enrolled in that period using a given compound
(data derived from Sponsor displays ISS SUB.20A/B/C, ISS update)

Titration requirements

USA-87

The mean daily dose of Duragesic during the primary treatment period was 1.4 ±0.15μg/kg/hour for pediatric patients under 6 years old, 1.23 ±0.13 μg /kg /hour for pediatric patients between 6 and 12 years old and 0.89 ±0.08 μg /kg /hour for pediatric patients over 12 years old.

Duragesic dose increased gradually during the primary treatment period for all age groups. When the pediatric patients were divided into those with malignant disease and those with non-malignant disease, the increase in average Duragesic dose was clearly driven by the former group.

Seventy-seven of the 199 patients required their first dose titration during the primary treatment period, after an average of five days.

- The five (19%) pediatric patients less than 6 years old averaged 7.6 days (median 7 days with a range from 4 to 13 days) before requiring a dose change. The median titration dose was 2.1 μg/h/kg (range 1.6-4.5 μg/h/kg). No subsequent titrations were reported for this group during the primary treatment period.
- The twenty-four (36%) pediatric patients aged 6- 12 years old averaged 6.4 days (median 4 days with a range from 2 to 13 days) before requiring a dose change. The median titration dose was 1.7 μg/h/kg (range 0.6-7.9 μg/h/kg).
- The forty-eight (47%) pediatric patients over 12 years old required a dose change after an average of 5 days (median 4 days with a range from 4 to 10 days). The median titration dose was 1.2 μg/h/kg (range 0.4-4.3 μg/h/kg).

The average time until subsequent titration was needed for patients between the ages of 6 and 16 was 3.8 days, with a median dose adjustment of 50 μg/h (range 25-200 μg/h) during the primary treatment period.

Evaluation of the 130 pediatric patients who entered the extension period (after 15 days of primary treatment) revealed that 36 pediatric patients needed further titration. The five pediatric patients who were age 6 years or younger (28%) went an average of 22 days before needing a titration, the median was 12 days with a range of 3 to 56 days. The median titration dose was 3.3 µg/h/kg (range 2.7-5.8 µg/h/kg). The 17 pediatric patients who were aged 6-12 years (39%) went an average of 13 days before needing a titration, the median was 6 days with a range of 1 to 63 days. The median titration dose was 3.0 µg/h/kg (range 0.4-15.8 µg/h/kg). The 14 oldest pediatric patients (21%) went an average of 19 days before requiring a dose titration, the median was 21 days with a range of 1 to 38 days. The median titration dose was 1.7 µg/h/kg (range 0.8-5.7 µg/h/kg).

INT-24

The protocol called for all patients in this study to begin with the 12.5 µg/h patch, however one patient began with a 37.5 µg/h patch.

Seventeen pediatric patients required their first dose titration during the primary treatment period, after five days of therapy on average. The average time until subsequent titration was needed was 3 days, with a median dose adjustment of 25 µg/h during the primary treatment period.

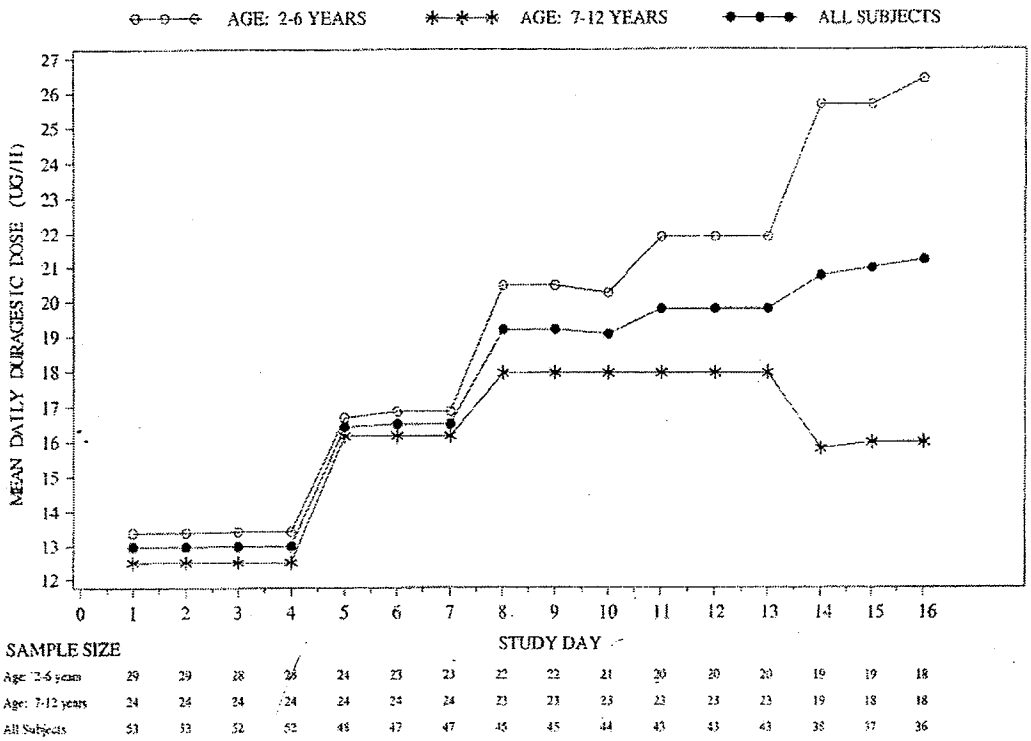
- The 8 pediatric patients (28%) under 6 years old went an average of 6 days (median 6 days with a range from 4 to 13 days) before requiring a dose change. The median titration dose was reported as 28.1 µg/h (range 25-81.3 µg/h). The median time to subsequent titration was 3 days, range 3-6 days.
- The 9 pediatric patients (38%) between 6-12 years old went an average of 5 days (median 4 days with a range from 4 to 7 days) before requiring a dose change. The median titration dose was reported as 25 µg/h (range 25-31.3 µg/h). The time to subsequent titration for all nine of these patients was 3 days.

Evaluation of the 10 pediatric patients who entered the extension period (after 15 days of primary treatment) revealed that only 4 pediatric patients needed further titration. The three pediatric patients who were age 6 years or younger went an average of 62 days before needing a titration, the median was 36 days with a range of 2 to 148 days. The one older child went 92 days before requiring a dose titration.

The increase in daily Duragesic dose over time for the primary treatment period became divergent at Day 7 when the dose for the younger pediatric patients began increasing while the requirement for the older pediatric patients reached a plateau then decreased (see graph EFF.05). This is likely attributable to disease progression in the younger age group.

During the primary treatment period, rescue dosing was higher for the pediatric patients aged 7-12 until day 8 when rescue dosing for the younger pediatric patients increased (see graph EFF.08). This increase in rescue medication use is likely attributable to disease progression in the younger age group.

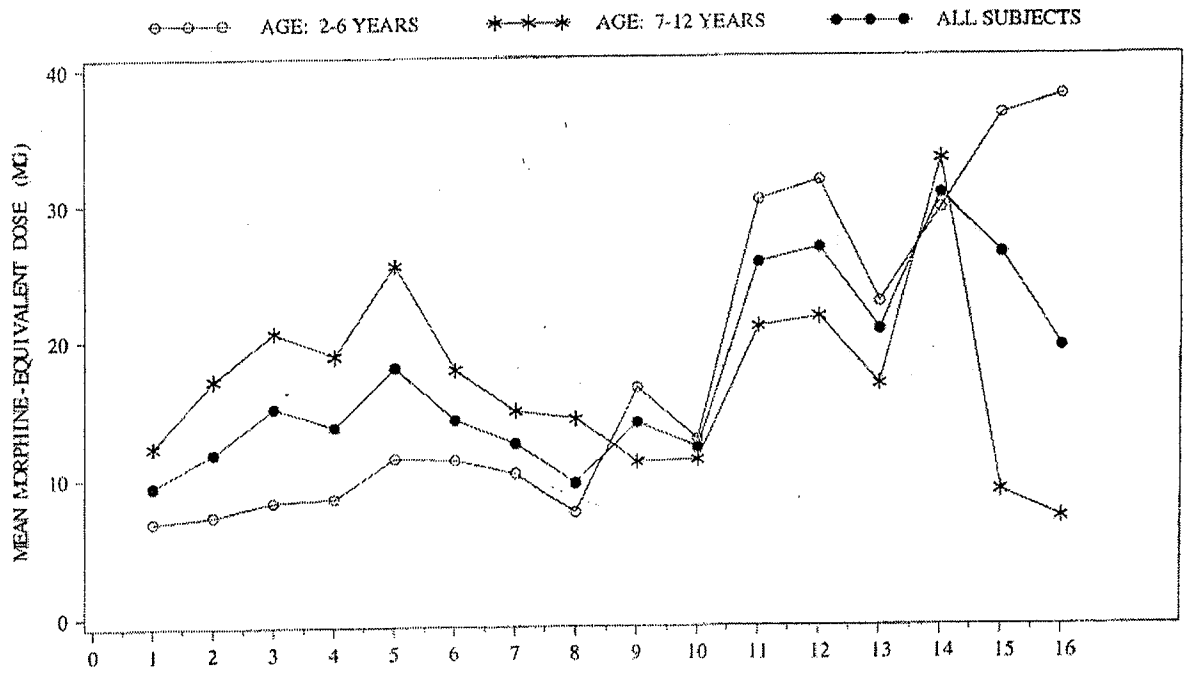
GRAPH EFF.05A AVERAGE DAILY DURAGESIC DOSAGE OVER TIME
FOR THE PRIMARY TREATMENT PERIOD--OVERALL AND BY AGE CATEGORY
POPULATION: INTENT-TO-TREAT



SAMPLE SIZE

Age: 2-6 years	29	29	28	28	24	23	23	22	22	21	20	20	20	19	19	18
Age: 7-12 years	24	24	24	24	24	24	24	23	23	23	23	23	23	19	18	18
All Subjects	53	53	52	52	48	47	47	45	45	44	43	43	43	38	37	36

GRAPH EFF.08A AVERAGE MORPHINE-EQUIVALENT DOSAGE OF RESCUE MEDICATION TAKEN OVER TIME
FOR THE PRIMARY TREATMENT PERIOD--OVERALL AND BY AGE CATEGORY
POPULATION: INTENT-TO-TREAT



SAMPLE SIZE

Age: 2-6 years	17	18	12	11	10	11	10	11	8	9	5	5	6	7	5	2
Age: 7-12 years	16	15	15	11	9	9	9	5	7	6	5	5	3	3	3	3
All Subjects	33	33	27	22	19	20	19	16	15	15	10	10	9	10	8	5

GBR-14

The protocol called for a minimum starting dose of 25 µg/h, though initial dosing was based on the previous opioid requirements. The majority (n=34, 83%) of the subjects in this study started with a 25µg/h patch. Five subjects started with 50µg/h Duragesic. One started with 75µg/h Duragesic and one started with 150 µg/h Duragesic. The median first patch size/body weight ratio was 1.31 µg/kg/hr, range 0.37-2.38 µg/kg/hr.

Nine patients did not require dose increases during the initial fifteen day treatment phase. Of the remaining 26 patients, twelve (34%) required two dose increases. Five subjects (14%) required only one increase, while nine (38%) required three or more increases. The median last patch size/body weight ratio was 1.82 µg/kg/hr, range 0.66-8.56 µg/kg/hr.

FRA-4

This was a single dose pharmacokinetic study, using 25 µg/h Duragesic in postoperative patients. No dosing or titration information can be derived from this study.

Summary of dosage/titration findings

These trials provided adequate safety data to support the use of a 25 µg/h patch in children with a previous oral morphine equivalent requirement of 45-134 mg. The titration method, which increased Duragesic by 25µg/h for each 90mg of morphine or equivalent opioid taken as rescue medication, was well tolerated.

While in 1.5- 5 year old non-opioid patients (FEN-FRA-04), the plasma fentanyl levels were approximately twice as high as that of adult patients, in patients over 5 years old the pharmacokinetic parameters were similar to adults. These pharmacokinetics findings were taken into account in the determination of the dosing recommendations for pediatric patients.

These studies do not provide sufficient information to adequately assess the proper

Concomitant Medications

The entire population was evaluated for the use of concomitant medications, n=293. The majority of the patients were taking at least one other medication while on study-99.5%. The sponsor reports no clinical evidence of drug-drug interaction between Duragesic and concomitant medications.

Antiemetics

The 171 subjects who received antiemetics experienced a higher overall incidence of adverse events than the 122 subjects who did not (95% vs. 85 %). The major category of AE affected was gastrointestinal system disorders (65% vs. 52%) such as nausea, vomiting, abdominal pain. The pediatric patients using antiemetics were also more likely to have red blood cell disorders (22% vs. 10 %) and/or white blood cell and reticuloendothelial disorders (18% vs 6%).

CNS Sedatives

The 140 subjects who received CNS Sedatives experienced a higher overall incidence of adverse events than the 153 subjects who did not (96% vs. 86 %). The major category of AE affected was gastrointestinal system disorders (71% vs. 48%) such as nausea, vomiting. A disparity was also seen in general body as a whole disorders (57% vs. 48%). Convulsions (6%) and tremor (4%) were only seen in those pediatric patients receiving CNS sedatives, though the incidence of Central and peripheral nervous system disorders was also higher over all (35% vs. 24%). Respiratory disorders were higher in the group of pediatric patients receiving CNS sedatives, (39% vs. 19%). In the subcategory respiratory depression the incidence was almost equal (2% vs. 3%) and in the subcategory respiratory insufficiency, the incidence was slightly higher in the group that was not using CNS sedatives (1% vs. 2%). Pediatric patients using concomitant CNS sedatives had a higher incidence of skin and appendages disorders (38% vs. 22%), and psychiatric disorders (35% vs. 16%) with increased incidence of both somnolence (11% vs. 4%) and agitation (8% vs. 1%). Urinary tract disorders (26% vs. 9%) were more frequent in this group as were vision disorders (13% vs. 3%), Cardiovascular disorders (12% vs. 7%), musculoskeletal (10% vs. 5%), application site disorders (12% vs. 1%), and liver and biliary system disorders (7% vs. 3%). Both red blood cell disorders (14% vs. 19%) and white cell and RES disorders (9% vs. 17%) were less frequent.

Chemotherapy

The 95 subjects who received chemotherapy experienced a higher overall incidence of adverse events than the 198 subjects who did not (96% vs. 88 %). Again the major area affected is gastrointestinal system disorders (64% vs. 57%) with differences in vomiting, nausea and abdominal pain. As might be expected, body as a whole disorders, (59% vs. 49 %), resistance mechanism disorders (30% vs. 19%), platelet/bleeding and clotting disorders (23% vs. 17%), red blood cell disorders (23% vs. 14%), and white cell and RES disorders (23% vs. 9%) were all more common in this population. Skin and appendages disorders (22% vs. 31%), cardiovascular disorders (6% vs. 11%) and psychiatric disorders (18% vs. 28%) were all less common.

IX. Use in Special Populations

A. Evaluation of Sponsor's Gender Effects Analyses and Adequacy of Investigation

Both male and female patients were adequately represented in the study populations. When analyzed by gender approximately equal numbers of boys and girls had adverse events (94% vs. 86%). In most cases the incidence rates for a given AE were approximately equal. However there were a few exceptions, although the nature of thtese differences does not have apparent clinical significance.

Boys had a greater incidence of, dyspnea (6% vs. 3 %), somnolence (9% vs. 4%), insomnia (7% vs. 4%), bacterial infection (6% vs. 3%), and sepsis (5% vs. 2%).

Girls had a greater incidence of peripheral edema (8% vs. 3%), headache (19% vs. 14%), erythematous rash (6% vs. 3%), diaphoresis (5% vs. 2%), hypokalemia (6% vs 3%), urinary tract infections (7% vs. 3%), and conjunctivitis (5% vs. 2%).

B. Evaluation of Evidence for Age, Race, or Ethnicity Effects on Safety or Efficacy

Ethnicity was only recorded for studies FEN-USA-87 and FEN-INT-24. The majority of the pediatric patients enrolled were white, hispanic or black. It should be noted that the hispanic category can comprise a mixture of pediatric patients, some of whom would be considered white, others who would be considered black. Ten pediatric patients were classified as of other ethnic groups. Those ten pediatric patients will not be included in further discussion due to small numbers per category.

While for most adverse events the incidence rates were approximately equal there were a few disparities as shown in Table 17. The majority of the patients had malignancies but the incidence was not equal across ethnic groups. The percentage of white patients with malignancies was higher than that of either black or hispanic patients (81%, 56%, 66% respectively). The higher incidence of nausea and anemia in white patients might be related to the higher proportion of patients with malignancies receiving oncologic treatment. The higher incidence of rhinitis, insomnia, anorexia and nervousness in Hispanic patients can not be explained by review of the provided materials. The reporting of only two black children with anemia seems odd in a population with 13 known sickle cell anemia patients but reporting varied by both site and investigator's determinations of whether an adverse event was treatment emergent.

Table 17:
Adverse events divided by ethnicity

	White (n=156)	Hispanic (n=45)	Black (n=41)
Number of subjects with AE	141 (90%)	42 (93%)	33 (80%)
Nausea	41 (29%)	6 (14%)	3 (9%)
Abdominal pain	19 (13%)	9 (21%)	6 (18%)
Constipation	20 (14%)	7 (17%)	3 (9%)
Diarrhea	17 (12%)	9 (21%)	5 (15%)
Hematemesis	2 (1%)	3 (7%)	2 (6%)
Fever	60 (43%)	13 (31%)	11 (33%)
Pain	18 (13%)	7 (17%)	3 (9%)
Edema	11 (8%)	1 (2%)	2 (6%)
Dyspnea	6 (4%)	5 (12%)	2 (6%)
Rhinitis	3 (2%)	6 (14%)	0
Pharyngitis	5 (4%)	3 (7%)	0
Respiratory depression	2 (1%)	3 (7%)	1 (3%)
URI	4 (3%)	3 (7%)	0

Table 17: Adverse events divided by ethnicity			
	White (n=156)	Hispanic (n=45)	Black (n=41)
Number of subjects with AE	141 (90%)	42 (93%)	33 (80%)
Pruritis	16 (11%)	6 (14%)	6 (18%)
Rash	7 (5%)	4 (10%)	2 (6%)
Diaphoresis	4 (3%)	3 (7%)	2 (6%)
Headache	27 (19%)	7 (17%)	5 (15%)
Tremor	3(2%)	1 (2%)	2 (6%)
Insomnia	4 (3%)	7 (17%)	3 (9%)
Anorexia	5 (4%)	6 (14%)	1 (3%)
Anxiety	7 (5%)	3 (7%)	0
Nervousness	1 (1%)	6 (14%)	0
Agitation	0	3 (7%)	0
Hallucinations	1 (1%)	0	2 (6%)
Sepsis	5 (4%)	1 (2%)	2 (6%)
Bacterial infection	4 (3%)	3 (7%)	4 (12%)
Anemia	33 (23%)	3 (7%)	2 (6%)
Granulocytopenia	11 (8%)	5 (12%)	0
Hypotension	3 (2%)	2 (5%)	3 (9%)
Conjunctivitis	7 (5%)	1 (2%)	1 (3%)
Application site reaction	11 (8%)	5 (12%)	1 (3%)
Cardiac failure	0	0	3 (9%)
Cardiac arrest	0	2 (5%)	1 (3%)

C. Evaluation of Pediatric Program

This application is for the addition of pediatric information to the Duragesic label.

D. Comments on Data Available or Needed in Other Populations

There was no information on hepatic or renal insufficiency requested or provided.

X. Conclusions and Recommendations

A. Conclusions

Duragesic (fentanyl transdermal patch, NDA 19-813) is an opioid analgesic approved for use in persons over the age of 12 years.

The Sponsor has submitted this supplemental NDA in response to a pediatric written request issued by the FDA. The sponsor has met the objectives of the written request having demonstrated safe use of the product in pediatric patients as well as a safe and appropriate conversion method to Duragesic from oral and parenteral opioid therapies.

The Sponsor submitted three open-label studies of the safety and pharmacokinetics of Duragesic in the pediatric patient population. FEN-USA-87, was an open-label, multi-center, single-arm, nonrandomized study in patients age 2 to 16 years. All of the pediatric patients had received previous opioid treatment for pain. The initial Duragesic dose was calculated based on the opioid analgesic requirement from the previous 24 hours, with titration every 72 hours as necessary. FEN-INT-24 was an open-label, multi-center, single-arm, nonrandomized study in patients age 2 to 12 years. An initial patch of 12.5 µg/h was to be placed on each subject, with replacement every 72 hours and titration as needed, based on use of rescue medication and pain assessments. FEN-GBR-14 was an open-label, multi-center, single-arm, nonrandomized study. The initial Duragesic dose was based on the opioid analgesic requirement from the previous 24 hours, with titration every 72 hours as necessary. Additional pharmacokinetic information was obtained from FEN-FRA-4, an open-label, single dose study in eight patients between the ages of one and five years.

The majority of the pediatric patients who participated in these studies were male (n=176, 60.1 %), and lived outside of the United States of America (n=177, 60.4%). Most of the pediatric patients were in the first decade of life, with a mean age of 9.7 years (range 1-16). Of the 241 pediatric patients for whom Tanner staging was assessed, most were preadolescent i.e. Tanner stage 1 (54.5% of females, 61.3% of males). The majority of the pediatric patients (74%) had pain related to an underlying malignancy or its treatment.

These open-label trials, which did not address efficacy, demonstrated an adverse event profile in pediatric patients which is similar to the one seen in adults. Over half of the subjects (n=166, 57%) had at least one serious adverse event (SAE). Of the SAEs that could be attributed to study drug, none were unexpected for a product containing fentanyl.

The use of fentanyl in conjunction with CNS sedatives, anti-emetic therapy, and/or chemotherapy was associated with a higher incidence of adverse events. No unexpected abnormal signal was noted on review of concomitant medications in this population so the general contraindications/warnings regarding concomitant medications will be acceptable. The known interaction with cytochrome P450 will be noted as part of general labeling for fentanyl products.

The emergence of opiate withdrawal symptoms on conversion from morphine to fentanyl has been reported in adult as well as pediatric patients. The package labeling should include specific symptoms and cautions to heighten awareness of these risks in the initial three days of Duragesic use. It should specifically be noted that these symptoms may occur in conjunction with adequate pain control. Agitation and insomnia can be associated with either withdrawal or toxicity and will have to be evaluated for each individual patient in context.

As there is not currently a 12.5µg/h patch available, patients requiring less than 45mg of morphine or equivalent opioid medications are not appropriate candidates for Duragesic therapy. The titration method, which increased Duragesic by 25µg/h for each 90mg of morphine or equivalent opioid taken as rescue medication, was well tolerated. These studies do not provide sufficient information to adequately assess the proper method of dosing an opioid naïve pediatric patient with Duragesic.

B. Recommendations

The 12.5µg/h strength and a dose of 125µg/h may be confused. It is recommended that in the development of a 12.5µg/h patch the sponsor should consider making the lowest strength patch distinctive to reduce the risk for error. One approach would be to evaluate bioequivalence of the

XI. Appendix

A. Adverse events in pediatric patients that did not occur in the context of a clinical trial

Age/Sex	Description of AE
3/?	Sat on patch of unknown strength. Death from respiratory failure.
3/M	Upon increasing from 25µg/h to 50µg/h, noted to have raised broken red skin at application site
6/M	Ingested some of gel from 25µg/h patch.
7/F	On 25µg/h patch noted to have shivering and trembling
8/M	On 50µg/h patch noted to have nightmares
8/M	25µg/h patch for AIDS related pain. Insomnia so patch was discontinued.
9/M	Applied 50µg/h patch prescribed for his parent. No medical intervention was given.
10/M	Application site reaction (erythematous/papular rash) while on 200µg/h
10/M	On 50µg/h patch noted to have facial swelling, shortness of breath and stridor
11/F	Pharmacologist reported that a physician ordered 25µg/h patch with instructions to cover half the patch to obtain 12.5µg/h dose. No AE noted.
11/F	On 25µg/h patch for pruritis and HIV dermatitis, had worsening of pruritis.
11/M	On 25µg/h patch for metastatic Ewing's sarcoma of leg. On day 1 of therapy pain relieved enough to allow cross-country skiing expedition. On Day 2, he was drowsy, nauseated and felt unwell. The patch was removed.
12/M	Vomiting while wearing a 25µg/h patch
12/M	Swelling from T4 dermatome upwards which resolved a few hours after removing the patch
12/F	25µg/h patch for AIDS related pain. Hallucinations experienced after patch was discontinued.
12/F	100µg/h for cancer pain. Experienced seizures followed by respiratory depression.
13/F	Chewed 50µg/h patch. No medical intervention was given.
13/M	On a 50µg/h patch for sarcoma/mucositis, on reduction to a 25µg/h patch had withdrawal symptoms
14/F	Took a hot bath while wearing patch-Application site reaction with burning and soreness
14/F	Fluid on lungs, decreased appetite, difficulty breathing, withdrawal symptoms
14/M	Applied 25µg/h patch which was not prescribed for him. No medical intervention was given.
14/M	Ingested used 25µg/h patch. No medical intervention was given.
14/M	Ingested 75µg/h patch. Complaints of pruritis and emesis.

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A. Adverse events in pediatric patients that did not occur in the context of a clinical trial (continued)

14/M	Dosage strength increased from 25µg/h to 100 over 2 months. At the last increase from 75µg/h to 100µg/h, his agitation became extreme and was accompanied by hyperactivity and insomnia. These symptoms resolved 24 hours after removal of the patch.
15/F	50 µg/h patch given for postoperative pain. Noted to have a respiratory rate of 6, hypotension and somnolence. Recovered after hospitalization in ICU and treatment with naloxone.
15/M	100 µg/h patch not effective in relieving pain
15/M	On increase from 25µg/h to 50µg/h, experienced nausea, confusion, inability to concentrate and inability to stand. Symptoms resolved once decreased to 25µg/h
15/F	Died of alveolar rhabdomyosarcoma while on 100 µg/h patch
15/F	Titrated from 25µg/h to 75µg/h then titrated to zero. Within days, anxiety, abdominal pain, chest pain radiating to arms and temporary loss of vision were reported.
15/M	While on 25µg/h patch experienced urinary retention, lethargy, vomiting and headache
Child/M	Child's grandmother was wearing a patch which came off and attached itself to her grandson. The child became ill and was taken to the hospital.
Adolescent /F	100 µg/h patch causing application site reaction with dry scaly skin under patch
Adolescent /F	100 µg/h patch causing red blotchy rash

B. Diagnoses for pediatric patients included in the ISS

Diagnosis	# (%)	USA-87	INT-24	GBR-14
Malignancy	218 (74%)	132	50	36
Hematologic	64 (29%)	48	12	4
Non-hematologic	156 (71%)	86	38	32
Non-malignancies	75 (26%)			
Burns		1	0	0
Dermatomyositis		1	0	0
Duchenne's muscular dystrophy		0	0	2
Orthopedic malformation-multiple syndromes		9	0	0
Dysuria		1	0	0
Fibromyalgia		1	0	0
Friedrich's ataxia		2	0	1
Gaucher's disease		1	0	0
GVHD		1	0	0
Hepatitis		1	0	0
JRA		5	0	0
Liver transplant		1	0	0
Metachromatic leukodystrophy		0	1	0
Microvillus inclusion disease		1	0	0
Migraines		2	0	0
Mucositis (non-oncologic)		1	0	0
Necrotizing pneumonia		1	0	0
Neurofibromatosis		2	0	0
Olmsted syndrome		0	1	0
Orthopedic injury NOS		1	0	0
Pancreatitis		11	0	0
Pleurisy		1	0	0
Postherpetic abdominal pain		1	0	0
Proteus syndrome		1	0	0
Sanfilippo's syndrome		1	0	1
Septic arthritis/osteomyelitis		1	0	0
Severe limb pain		1	0	0
Sickle Cell Disease		13	0	0
Spondylolithesis		1	0	0
Static encephalopathy		0	0	1
Subsclerosing panencephalitis		0	1	0
SLE		3	0	0
Tethered cord		1	0	0
Viral myositis		1	0	0

C. Patients who discontinued for reasons other than death or adverse events

Study / Patient #	Age/sex	reason	Study day	Dose
USA-87 A30012	11/F	Other: leaving the country	49	1.79 µg/kg/h
USA-87 A30014	14/M	Consent withdrawn	134	1.35 µg/kg/h
USA-87 A30019	11/M	Inadequate analgesia	1	1.71µg/kg/h
USA-87 A30023	15/M	Needed increased pain medicine	22	4.41µg/kg/h
USA-87 A30027	10/F	"makes pt feel bad, not effacacious"	15	0.5 µg/kg/h
USA-87 A30034	9/M	Other: patch removed	23	0.57 µg/kg/h
USA-87 A30037	7/F	Other: pain decreased	10	1.19 µg/kg/h
USA-87 A30040	13/M	Other: pain decreased	19	0.47 µg/kg/h
USA-87 A30045	6/M	Insufficient response	3	4 µg/kg/h
USA-87 A30049	12/M	Other: MD chose to wean fentanyl	58	0.33 µg/kg/h
USA-87 A30053	10/M	Non-compliant	17	0.68 µg/kg/h
USA-87 A30055	15/F	Insufficient response	7	0.72 µg/kg/h
USA-87 A30059	15/M	Insufficient response	33	0.54µg/kg/h
USA-87 A30065	9/M	Needed change in pain med	28	4.29 µg/kg/h
USA-87 A30067	13/M	Other: titrated off opioids	60	0.31 µg/kg/h
USA-87 A30076	15/M	Ineligible to continue trial	13	0.36 µg/kg/h
USA-87 A30082	10/M	Other: pain decreased	19	0.36 µg/kg/h
USA-87 A30084	7/M	Non-compliant	13	0.52 µg/kg/h
USA-87 A30086	12/M	Other: pain decreased	22	0.21 µg/kg/h
USA-87 A30087	10/M	Insufficient response	20	µg/kg/h

C. Patients who discontinued for reasons other than death or adverse events (cont.)

USA-87 A30089	2/M	Insufficient response	324	5 µg/kg/h
USA-87 A30091	9/F	Withdrew consent: felt better with morphine	55	0.806 µg/kg/h
USA-87 A30096	7/F	Insufficient response	641	14.88 µg/kg/h
USA-87 A30098	10/M	Insufficient response	6	1.85µg/kg/h
USA-87 A30099	11/F	Insufficient response	105	2.56 µg/kg/h
USA-87 A30100	7/M	Other: pain decreased	187	0.69 µg/kg/h
USA-87 A30103	1/F	Ineligible to continue trial: Age	1	3.57 µg/kg/h
USA-87 A30104	15/M	Ecchymosis	91	7.24 µg/kg/h
USA-87 A30105	13/F	Ineligible to continue trial	123	0.32 µg/kg/h
USA-87 A30106	15/F	Insufficient response	87	3.19 µg/kg/h
USA-87 A30122	5/F	Other: stopped using study drug	31	3.13 µg/kg/h
USA-87 A30134	2/M	Other: Needed increased pain medicine	22	0.96 µg/kg/h
USA-87 A30135	14/F	Other: pain decreased	32	
USA-87 A30136	9/F	Other: Needed increased pain medicine	25	0.74 µg/kg/h
USA-87 A30138	11/F	Withdrew consent: mother chose not to wait on pharmacy	25	0.83 µg/kg/h
USA-87 A30149	3/F	Other: pain decreased	19	0.89 µg/kg/h
USA-87 A30150	7/F	Insufficient response	22	4.55 µg/kg/h
USA-87 A30155	7/M	Needed patch changes q48 hours	69	2.5 µg/kg/h
USA-87 A30158	14/M	Other: obtained patch off study	250	0.71 µg/kg/h
USA-87 A30161	14/M	Withdrew consent: tired of collecting data	69	3.70 µg/kg/h
USA-87 A30162	10/M	Withdrew consent: did not want to stay in hospital	3	0.57 µg/kg/h

C. Patients who discontinued for reasons other than death or adverse events (cont.)

USA-87 A30183	8/M	Other: opioid need completed	22	0.42 µg/kg/h
USA-87 A30184	13/M	Other: patches completed, care resumed by PMD	28	0.18 µg/kg/h
USA-87 A30185	15/M	Other: trial end	18	0.39 µg/kg/h
USA-87 A30189	8/M	Other: pain diminished	27	0.5µg/kg/h
USA-87 A30191	13/M	Other: pain diminished	59	0.13µg/kg/h
USA-87 A30192	14/M	Withdrew consent: mother did not want to keep records	19	1.16 µg/kg/h
USA-87 A30193	14/F	Other: patient weaned off drug	19	0.52 µg/kg/h
USA-87 A30199	13/M	Non-compliant	2	0.61 µg/kg/h
USA-87 A30200	14/M	Insufficient response	23	2.92 µg/kg/h
USA-87 A30201	2/M	Other: patient weaned off drug	61	0.89 µg/kg/h
USA-87 A30210	8/M	Withdrew consent: guardian decision	22	1.92 µg/kg/h
USA-87 A30211	9/M	Needed more frequent patch changes	19	3.79 µg/kg/h
USA-87 A30212	14/M	Withdrew consent: didn't wish to participate further	18	1.17 µg/kg/h
USA-87 A30217	2/F	Other:2 IP lost; pt dc	61	3.26µg/kg/h
USA-87 A30223	8/M	Other:MD felt pt no longer needed	13	0.42µg/kg/h
USA-87 A30224	4/F	Ineligible to continue trial	30	2.5µg/kg/h
USA-87 A30225	3/M	Other: fentanyl available off label	37	1.56µg/kg/h
USA-87 A30336	12/M	Other: fentanyl drip started	22	0.53µg/kg/h
USA-87 A30337	12/M	Other: opioid need ended	46	0.3µg/kg/h
USA-87 A30338	12/M	Other: medication available off label	21	1.72µg/kg/h
USA-87 A30339	14/F	Withdrew consent-"tired of wearing patches"	40	2.38 µg/kg/h

C. Patients who discontinued for reasons other than death or adverse events (cont.)

USA-87 A30342	15/F	Ineligible to continue trial	22	0.72µg/kg/h
USA-87 A30343	15/F	Other: pain decreased	19	0.27µg/kg/h
USA-87 A30346	13/M	Other:tumor removed	120	0.33 µg/kg/h
USA-87 A30355	13/M	Ineligible to continue trial	22	1.92 µg/kg/h
USA-87 A30373	16/F	Ineligible to continue trial	1	0.25µg/kg/h
USA-87 A30384	15/F	Ineligible to continue trial	37	0.2µg/kg/h
USA-87 A30388	12/F	Ineligible to continue trial	35	1.25µg/kg/h
USA-87 A30390	11/M	Other: pain diminished	36	0.96 µg/kg/h
USA-87 A30391	9/M	Ineligible to continue trial	28	0.69 µg/kg/h
USA-87 A30392	6/F	Ineligible to continue trial	97	0.74 µg/kg/h
USA-87 A30397	5/F	Insufficient response	193	1.14 µg/kg/h
USA-87 A30403	12/M	Other: pain diminished	19	0.38 µg/kg/h
USA-87 A30409	13/F	Withdrew consent-refused to wear patches	49	1.67 µg/kg/h
USA-87 A30412	13/F	Withdrew consent-wants greater flexibility with patch management	30	0.61 µg/kg/h
USA-87 A30413	2/M	Other:ready to be tapered off opioids	21	0.96 µg/kg/h
USA-87 A30418	15/M	Ineligible to continue trial	94	0.17 µg/kg/h
USA-87 A30419	15/M	Ineligible to continue trial	76	0.33 µg/kg/h
USA-87 A30423	9/M	Ineligible to continue trial	55	0.54 µg/kg/h
USA-87 A30425	15/M	Ineligible to continue trial	49	0.27 µg/kg/h
USA-87 A30429	5/M	Other: no need for constant narcotic	22	0.5 µg/kg/h
USA-87 A30430	12/M	Other: no need for constant narcotic	18	0.28 µg/kg/h

C. Patients who discontinued for reasons other than death or adverse events (cont.)

USA-87 A30455	13/M	Other: opioid taper	22	0.31 µg/kg/h
USA-87 A30456	11/M	Other: opioid taper	25	0.39 µg/kg/h
USA-87 A30481	14/M	Ineligible to continue trial	34	0.96 µg/kg/h
USA-87 A30501	2/M	Other, likely discharge	3	2.08 µg/kg/h
USA-87 A30502	15/F	Other: no longer needs patch	201	0.19 µg/kg/h
USA-87 A30513	3/F	Other: more stable using methadone rescue	37	2.78 µg/kg/h
USA-87 A30518	10/M	Other: pt switched to commercial drug	22	0.39 µg/kg/h
USA-87 A30528	12/F	Other: leaving the country	25	4.35 µg/kg/h
USA-87 A30532	14/F	Lost to followup	139	0.51µg/kg/h
USA-87 A30538	10/M	Ineligible to continue trial	19	2.84 µg/kg/h
USA-87 A30539	5/M	Ineligible to continue trial	19	0.57 µg/kg/h
USA-87 A30540	14 /F	Insufficient response	171	4.25 µg/kg/h
USA-87 A30548	15/F	Other: rheumatology-pt off patch give methadone	32	1.72 µg/kg/h
INT-24 A30003	11/F	Insufficient response	13	1.71 µg/kg/h
INT-24 A30012	5/M	Other: not happy with plaster of patch	28	0.65 µg/kg/h
INT-24 A30032	5/M	Withdrew consent: patch fell off	4	0.69 µg/kg/h
INT-24 A30035	12/F	Insufficient response	37	0.8 µg/kg/h
INT-24 A30054	5/F	Insufficient response	54	1 µg/kg/h
INT-24 A30055	7/M	Ineligible to continue trial	77	0.46 µg/kg/h
INT-24 A30056	10/M	Other: pain decreased	14	0.42 µg/kg/h
INT-24 A30057	2/F	Ineligible to continue trial	197	1.04 µg/kg/h

C. Patients who discontinued for reasons other than death or adverse events (cont.)

INT-24 A30058	9/M	Ineligible to continue trial	37	0.43 µg/kg/h
INT-24 A30059	9/F	Ineligible to continue trial	31	0.69 µg/kg/h
INT-24 A30077	12/M	Other: pain decreased	249	0.32 µg/kg/h
INT-24 A30092	12/M	Other: pain decreased	13	0.48 µg/kg/h
INT-24 A30095	10/M	Other:pain decreased	13	0.31 µg/kg/h
INT-24 A30158	11/F	Insufficient response	7	0.69 µg/kg/h
INT-24 A30161	4/M	Insufficient response	4	0.54 µg/kg/h
GBR-14 007	6/M	Uncontrolled pain	49	33.33µg/kg/h
GBR-14 013	3/F	Escalation of pain	2	1.6 µg/kg/h
GBR-14 016	15/F	Other: ran out of diary forms-did not contact investigator	49	0.68 µg/kg/h
GBR-14 032	13/F	Withdrew consent	28	2.31 µg/kg/h
GBR-14 033	12/M	Other:Rx changed to diamorphine by syringe driver	47	3.34 µg/kg/h
GBR-14 044	4/M	Other:Rx changed to SQ diamorphine and midazolam infusion	23	9.06 µg/kg/h
GBR-14 047	11/M	Other: pain decreased	31	0.79 µg/kg/h
GBR-14 048	10/M	Insufficient response	45	0.7 µg/kg/h
GBR-14 057	12/M	Insufficient response	1	1.96 µg/kg/h
GBR-14 062	10/M	Withdrew consent	43	0.66 µg/kg/h
GBR-14 063	12/M	Withdrew consent	17	0.51 µg/kg/h
GBR-14 075	15/M	Withdrew consent: fever	7	
GBR-14 077	6/M	Withdraw consent	14	3.56 µg/kg/h
GBR-14 101	15/M	Asymptomatic/cured	18	1.80 µg/kg/h

C. Patients who discontinued for reasons other than death or adverse events (cont.)

GBR-14 102	6/M	Uncontrolled pain	4	1.47µg/kg/h
GBR-14 104	16/M	Uncontrolled pain	13	4.36 µg/kg/h
GBR-14 105	6/M	Escalating pain	15	4.76 µg/kg/h

(Information derived from ISS/ISS update displays AE.12, SUB.03, and SUB .05)

D. Deaths

Study # / Patient#	Study Phase /Dose at onset of SAE	Age/ Sex	Adverse Event /Cause of death	Duration of treatment (days)	Duration off study before death (days)
USA-87 /A30007	Extension/175µg/h	15/M	Disease progression-lymphoma		
USA-87 /A30015	Treatment/50µg/h	11/F	Disease progression-carcinoma of the cervix		
USA-87 /A30023	Off study /last dose was 150µg/h	15/M	Respiratory insufficiency		
USA-87 /A30026	Extension/25µg/h	6/M	Disease progression-neuroblastoma		
USA-87 /A30028	Off study /last dose was 12.5µg/h	13/M	Progression of osteosarcoma		
USA-87 /A30042	Extension/12.5 µg/h	14/M	Disease progression-ALL		
USA-87 /A30045	Treatment/100µg/h	6/M	Disease progression-ALL		
USA-87 /A30054	Off study/last dose was 25µg/h	3/F	Disease progression-ALL		
USA-87 /A30064	Treatment/100µg/h	6/M	Disease progression-neuroblastoma		
USA-87 /A30065	Off study/last dose was 175µg/h	9/M	Disease progression-osteosarcoma		
USA-87 /A30070	Extension/325µg/h	10/F	Disease progression-neuroblastoma		
USA-87 /A30085	Extension/25µg/h	13/F	Disease progression-osteosarcoma		
USA-87 /A30093	Treatment/25µg/h	5/M	Disease progression-neuroblastoma		
USA-87 /A30095	Treatment/25µg/h	13/M	Disease progression-ALL		
USA-87 /A30096	Off study/last dose was 312.5µg/h	7/F	Disease progression-Wilms tumor		
USA-87 /A30097	Extension/75µg/h	11/M	Disease progression-ALL		
USA-87 /A30098	Off study/last dose was 25µg/h	10/M	Disease progression-Wilms tumor		
USA-87 /A30104	Extension/275µg/h	15/M	Disease progression-nasopharyngeal carcinoma		
USA-87 /A30122	Off study/last dose was 37.5µg/h	5/F	Disease progression-neuroblastoma		
USA-87 /A30134	Off study/last dose was 12.5	2/M	Disease progression-hepatoblastoma		
USA-87 /A30150	Off study/last dose was 100µg/h	7/F	Disease progression-teratoma		
USA-87 /A30163	Treatment/25µg/h	9/F	Disease progression-neuroblastoma		
USA-87 /A30174	Extension/12.5 µg/h	14/F	Disease progression- San Filippo's syndrome		
USA-87 /A30180	Treatment/75µg/h	11/M	Disease progression-ANLL		

D. Deaths (cont.)

Study # / Patient#	Study Phase /Dose at onset of SAE	Age/ Sex	Adverse Event /Cause of death	Duration of treatment (days)	Duration off study before death (days)
USA-87 /A30190	Extension/187.5µg/ h	10/F	Disease progression- extrarenal rhabdoid sarcoma		
USA-87 /A30192	Off study/last dose was 25µg/h	14/M	Disease progression- desmoplastic small round cell tumor		
USA-87 /A30194	Off study/last dose was 12.5µg/h	13/F	Disease progression-ANLL		
USA-87 /A30211	Off study/last dose was 125µg/h	9/M	GI hemorrhage in child with GVHD		
USA-87 /A30212	Off study/last dose was 75µg/h	14/M	GVHD		
USA-87 /A30217	Off study/last dose was 75µg/h	2/F	Optic glioma		
USA-87 /A30218	Off study/last dose was 12.5µg/h	6/M	Disease progression-ALL		
USA-87 /A30301	Extension/25µg/h	12/M	Disease progression- glioma		
USA-87 /A30313	Treatment/12.5µg/h	11/F	Disease progression- clear cell sarcoma of the kidney		
USA-87 /A30321	Treatment/25µg/h	15/M	Disease progression- NHL		
USA-87 /A30349	Treatment/12.5µg/h	3/M	Disease progression- undifferentiated carcinoma		
USA-87 /A30355	Off study/last dose was 87.5µg/h	13/M	Disease progression- renal carcinoma		
USA-87 /A30370	Off study/last dose was 12.5µg/h	9/F	Disease progression- neuroblastoma		
USA-87 /A30381	Extension/12.5µg/h	12/M	Disease progression- neuroblastoma		
USA-87 /A30389	Off study/last dose was 37.5µg/h	15/M	Disease progression- medulloblastoma		
USA-87 /A30393	Extension/62.5µg/h	7/F	Disease progression- Ewing's sarcoma		
USA-87 /A30394	Extension/100µg/h	2/M	Disease progression- rhabdomyosarcoma		
USA-87 /A30396	Off study/last dose was 50µg/h	13/F	Disease progression- NHL		
USA-87 /A30398	Extension/300µg/h	7/M	Disease progression- neuroblastoma		
USA-87 /A30400	Extension/25µg/h	14/M	Disease progression- glioblastoma		
USA-87 /A30408	Extension/75µg/h	10/M	Disease progression- NHL		
USA-87 /A30448	Extension/100 µg/h	13/M	Disease progression- Ewing's sarcoma		
USA-87 /A30466	Off study/last dose was 12.5µg/h	6/M	Disease progression- neuroblastoma		
USA-87 /A30467	Off study/last dose was 25µg/h	14/M	Disease progression- hepatoblastoma		

D. Deaths (cont.)

Study # / Patient#	Study Phase /Dose at onset of SAE	Age/ Sex	Adverse Event /Cause of death	Duration of treatment (days)	Duration off study before death (days)
USA-87 /A30468	Off study/last dose was 12.5µg/h	11/M	Disease progression-osteosarcoma		
USA-87 /A30469	Off study/last dose was 25µg/h	10/M	Disease progression-medulloblastoma		
USA-87 /A30473	Off study/last dose was 50µg/h	12/M	Disease progression-neuroblastoma		
USA-87 /A30477	Off study/last dose was 25µg/h	8/M	Disease progression- ALL		
USA-87 /A30481	Off study/last dose was 25µg/h	14/M	Disease progression-Ewing's sarcoma		
USA-87 /A30496	Extension/25µg/h	10/M	Disease progression- ALL		
USA-87 /A30501	Off study/last dose was 25µg/h	2/M	Disease progression- spinal cord rhabdoid tumor		
USA-87 /A30503	Off study/last dose was 162.5µg/h	11/M	Disease progression-Ewing's sarcoma		
USA-87 /A30504	Extension/<12.5µg/h	14/F	Disease progression-brainstem glioma		
USA-87 /A30535	Extension/50µg/h	6/M	Disease progression-neuroblastoma		
USA-87 /A30536	Treatment/25µg/h	15/F	Disease progression- ANLL		
USA-87 /A30548	Off study/last dose was 100µg/h	15/F	Hyperkalemia, multisystem organ failure		
INT-24 /30014	Treatment/12.5µg/h	2/F	Disease progression-retinoblastoma		
INT-24 /30048	Treatment/12.5µg/h	3/M	Disease progression-ALL		
INT-24 /30049	Extension/50µg/h	11/M	Disease progression-thyroid tumor		
INT-24 /30051	Extension/75µg/h	4/M	Disease progression-rhabdomyosarcoma		
INT-24 /30052	Extension/12.5µg/h	5/F	Disease progression-ependymoma		
INT-24 /30053	Off study /last dose was 12.5µg/h	5/M	Disease progression-ependymoma		
INT-24 /30078	Treatment /12.5µg/h	5/F	Disease progression-ependymoma		
INT-24 /30085	Extension/62.5µg/h	10/F	Disease progression-glioblastoma		
INT-24 /30091	Extension/12.5µg/h	5/M	Disease progression-neuroblastoma		
INT-24 /30093	Treatment/25µg/h	6/F	Disease progression-neuroblastoma		

D. Deaths (cont.)

Study # / Patient#	Study Phase /Dose at onset of SAE	Age/ Sex	Adverse Event /Cause of death	Duration of treatment	Duration off study before death (days)
INT-24 /30096	Treatment/200µg/h	3/F	Disease progression-encephalopathy		
INT-24 /30123	Off study/last dose was12.5µg/h	10/M	Disease progression-NHL		
INT-24 /30006	Treatment/12.5µg/h	2/M	Disease progression-neuroblastoma		
GBR-14 /01	Extension/400µg/h	15/F	Disease progression-neuroblastoma		
GBR-14 /08	Extension/100µg/h	18/M	Disease progression-Ewing's sarcoma		
GBR-14 /14	Extension/150µg/h	4/F	Disease progression-Wilms' tumor		
GBR-14 / 15	Extension/50µg/h	5/F	Disease progression-ALL		
GBR-14 /20	Extension/75µg/h	3/M	Disease progression-neuroblastoma		
GBR-14 /21	Extension/75µg/h	2/F	Disease progression- germ cell tumor		
GBR-14 /23	Treatment/75µg/h	6/M	Disease progression-T cell lymphoma		
GBR-14 /25	Extension/1400µg/h	14/M	Disease progression-Desmoplastic small round cell tumor of pancreas		
GBR-14 /26	Extension/100µg/h	6/M	Disease progression-Brainstem glioma		
GBR-14 /27	Extension/50µg/h	16/F	Chest infection, failure of the left ventricle		
GBR-14 /29	Treatment/25µg/h	16/M	Aspiration pneumonia		
GBR-14 /33	Off study/ last dose was 175µg/h	12/M	Disease progression-glioma		
GBR-14 /44	Off study/ last dose was 125µg/h	16/M	Disease progression-Rhabdomyosarcoma		
GBR-14 /45	Treatment/100µg/h	7/M	Disease progression-Rhabdomyosarcoma		
GBR-14 /46	Treatment/250µg/h	7/M	Disease progression-Rhabdomyosarcoma		
GBR-14 /49	Treatment/75µg/h	3/F	Disease progression-Supersellar teratoma		
GBR-14 /59	Treatment/25µg/h	17/F	Disease progression-Ovarian germ cell tumor		
GBR-14 /60	Extension /225µg/h	18/F	Disease progression-Clear cell sarcoma		
GBR-14 /61	Extension /75µg/h	14/M	Disease progression-Malignant Schwannoma		
GBR-14 /69	Treatment/25µg/h	17/M	Vomiting, Cardiac Arrest, ALL		

D. Deaths (cont.)

GBR-14 /76	Extension /50µg/h	14/M	Disease progression-Duchenne's muscular dystrophy
GBR-14 /104	Off study/ last dose was 300µg/h	16/M	Disease progression-PNET
GBR-14 /105	Off study/ last dose was 100µg/h	6/M	Disease progression-Neuroblastoma
GBR-14 /108	Treatment/50µg/h	3/M	Disease progression-PNET
GBR-14 /113	Off study/ last dose was 75µg/h	3/M	Disease progression-Clear cell sarcoma of kidney

E. Serious Adverse Events (occuring in > 2% of subjects)

Total number of subjects	293
Total number of subjects with SAE	166 (56.7%)
Fever	31 (19%)
Neuroblastoma	16 (10%)
Granulocytopenia	15 (9%)
Pain	14 (8%)
Sarcoma	13 (8%)
Vomiting	11 (7%)
Dyspnea	9 (5%)
Respiratory insufficiency	9 (5%)
Anemia	8 (5%)
Sepsis	8 (5%)
Thrombocytopenia	8 (5%)
Carcinoma	7 (4%)
Lymphocytic leukemia	7 (4%)
Malignant neoplasm	7 (4%)
Respiratory depression	7 (4%)
Nausea	7 (4%)
Pancytopenia	6 (4%)
Metastases NOS	6 (4%)
Abdominal pain	5 (3%)
Cardiac failure	5 (3%)
Epistaxis	5 (3%)
Pneumonia	5 (3%)
Somnolence	5 (3%)
Cardiac arrest	5 (3%)
Infection	5 (3%)
Leukemia	4 (2%)
Pancreatitis	4 (2%)
Dehydration	4 (2%)
Malignant brain neoplasm	3 (2%)
Acute leukemia	3 (2%)
Malignant lymphoma	3 (2%)
Renal carcinoma	3 (2%)
Hypokalemia	3 (2%)
Bacterial infection	3 (2%)
Diarrhea	3 (2%)
Stupor	3 (2%)

(ISS update-display AE.13AB)

E. **Serious Adverse Events (occuring in > 2% of subjects)**

SAE that occurred in 2 or fewer patients

Neoplasm: Teratoma, astrocytoma, cervix carcinoma, malignant hepatic neoplasm, granulocytic leukemia, neoplasm NOS, non-hodgkin's lymphoma, ovarian carcinoma, malignant neoplasm of the pharnyx, retinoblastoma, malignant thyroid neoplasm

Body as a whole-general disorders: Back pain, chest pain, multiple organ failure, allergic reaction, fatigue, ischemic necrosis, edema, rigors, serum sickness, syncope, withdrawal syndrome

Respiratory system disorders: Apnea, asthma, pulmonary infiltration, sinusitis, aspiration, pharnygitis, pneumothorax, pulmonary edema, respiratory disorder

Gastrointestinal disorders: Constipation, GI hemorrhage, mucositis NOS, bowel motility disorder, pseudomembranous colitis, duodenitis, dyspepsia, enteritis, gastritis, gastroenteritis, hematemesis, intraabdominal hemorrhage, intestinal obstruction, intestinal perforation, acquired megacolon, melena, esophagitis, decreased pancreatic secretion, stomatitis

Red blood cell disorders: Hemolysis, marrow depression

White cell and RES disorders: Leucopenia, leukocytosis

Resistance mechanism disorders: herpes zoster

Metabolic and nutritional disorders: Electrolyte abnormality, lactic acidosis, enzyme abnormality, hypercalcemia, hyperglycemia, hyperkalemia, hypoglycemia, hyponatremia, increased lipase, weight decrease

Secondary terms: Fall, medication error, procedural site reaction, spinal cord compression, surgical intervention

General cardiovascular disorders: blood pressure fluctuation, hypertension, hypotension, circulatory failure

Platelet, bleeding and clotting disorders: pulmonary embolism

Heart rate and rhythm disorders: tachycardia

CNS/PNS disorders: Convulsions, encephalopathy, headache, paralysis, coma, dizziness, hypertensive encepahlopathy, hypesthesia, peripheral neuropathy, tremor, vertigo, vocal cord paralysis, nervousness, personality disorder, abnormal thinking, cerebral hemorrhage

Urinary system disorders: acute renal failure, abnormal renal function, urethral disorder, abnormal urine

E. **Serious Adverse Events, continued (occuring in > 2% of subjects)**
SAE that occurred in 2 or fewer patients
Vascular disorders: cerebrovascular disorder, intracranial hemorrhage, deep thromophlebitis, vascular disorder, varicose vein

Liver and biliary system disorders: bilirubinemia, abnormal hepatic function, hepatocelluar damage, jaundice

Skin and appendages disorders: hyperkeratosis, pruritis, rash, skin disorder, skin ulceration

Vision disorders: diplopia, eye pain, miosis, abnormal vision

Collagen disorders: graft versus host disease, auto-anitbody response

Musculoskeletal disorders: pathological fracture, hemarthrosis, myopathy

Fetal disorders: hydrocephalus

Myo-, Endo-, pericardial and valve disorders: pericarditis, pericardial effusion

F. Adverse Events occurring in > 2% of subjects in either primary or extension treatment phase

	Primary (N=293) n (% of enrolled subjects)	Extension Phase (N=168) n (%of enrolled subjects)
Number with at least one adverse event[b,c]	255 (87)	133 (79)
Gastrointestinal system disorders	152 (59%)	74 (56%)
Vomiting	77 (30%)	35 (26%)
Nausea	55 (22%)	23(17%)
Abdominal Pain	31 (12%)	15 (11%)
Constipation	26 (10%)	16 (12%)
Diarrhea	23 (9%)	15 (11%)
Mucositis NOS	3 (1%)	5 (4%)
Hematemesis	6 (2%)	4 (3%)
Mouth dryness	4 (2%)	3 (3%)
GI disorder NOS	0	3 (3%)
Melena	1 (1%)	3 (3%)
Pancreatitis	1 (1%)	3 (3%)
Body as a whole	120 (47%)	71 (53%)
Fever	75 (29%)	41(31%)
Pain	24 (9%)	17 (13%)
Edema	10 (4%)	8 (6%)
Peripheral edema	9 (4%)	5 (4%)
Leg pain	6 (2%)	2 (2%)
Rigors	6 (2%)	0
Abdomen enlarged	5 (2%)	2 (2%)
Allergic reaction,	5 (2%)	7 (5%)
Asthenia	5 (2%)	0
Chest pain,	5 (2%)	3 (3%)
Fatigue,	5 (2%)	1 (1%)
Abnormal lab values	5 (2%)	1 (1%)
Syncope	4 (2%)	0
Central and peripheral nervous system	64 (25%)	33 (24%)
Headache	34 (13%)	15 (11%)
Tremor	6 (2%)	1 (1%)
Convulsions	5 (2%)	6 (5%)
Dizziness	4 (2%)	2 (2%)

F. Adverse Events occurring in > 2% of subjects in either primary or extension treatment phase (cont.)

	Primary (N=293) n (% of enrolled subjects)	Extension Phase (N=168) n (%of enrolled subjects)
Number with at least one adverse event[b,c]	255 (87)	133 (79)
Respiratory System disorders	53 (21%)	50 (38%)
Dyspnea	11 (4%)	7 (5%)
Coughing	7 (3%)	6 (1%)
Respiratory depression	5 (2%)	2 (2%)
Respiratory disorder	5 (2%)	0
Pharyngitis	3 (1%)	7 (5%)
Pneumonia	2 (1%)	10 (8%)
Rhinitis	4 (2%)	7 (5%)
URI	3 (1%)	6(5%)
Respiratory insufficiency	1 (1%)	4 (3%)
Bronchitis	1 (1%)	3 (3%)
Sinusitis	3 (1%)	3 (3%)
Skin and appendages disorders	71 (28%)	29 (22%)
Pruritis	32 (13%)	11 (8%)
Rash NOS	15 (6%)	4(3%)
Diaphoresis	10 (4%)	2 (2%)
Erythematous rash	8 (3%)	5 (4%)
Skin ulceration	5 (2%)	2 (1%)
Skin discoloration	2 (1%)	3 (3%)
Psychiatric disorders	54 (21%)	39 (29%)
Somnolence	16 (6%)	6 (5%)
Insomnia	11 (4%)	11 (8%)
Agitation	8 (3%)	7 (6%)
Anorexia	7 (3%)	8 (5%)
Anxiety	7 (3%)	5 (4%)
Depression	5 (2%)	0
Hallucinations	4 (2%)	2 (2%)
Nervousness	2 (1%)	4 (3%)
Confusion	1 (1%)	2 (2%)

F. Adverse Events occurring in > 2% of subjects in either primary or extension treatment phase (cont.)

	Primary (N=293) n (% of enrolled subjects)	Extension Phase (N=168) n (%of enrolled subjects)
Number with at least one adverse event[b,c]	255 (87)	133 (79)
Resistance mechanisms disorders	39 (15%)	42 (32%)
Infection	8 (3%)	12 (9%)
Bacterial infection	8 (3%)	6 (5%)
Sepsis	8 (3%)	5 (4%)
Moniliasis	7 (3%)	6 (5%)
Viral infection	2 (1%)	6 (5%)
Abcess	1 (1%)	4 (3%)
Herpes Simplex	1 (1%)	4 (3%)
Otitis media	1 (1%)	5 (4%)
Platelet, bleeding & clotting disorders	39 (15%)	24 (11%)
Thrombocytopenia	22 (9%)	14 (11%)
Epistaxis	10 (4%)	10 (8%)
Purpura	4 (2%)	1 (1%)
Metabolic and nutritional disorders	37 (15%)	28 (21%)
Hypokalemia	10 (4%)	6 (5%)
Hyperglycemia	5 (2%)	0
Hypocalcemia	5 (2%)	0
Hypomagnesemia	5 (2%)	6 (5%)
Acidosis	4 (2%)	1
Fluid overload	4 (2%)	4 (3%)
Dehydration	3 (1%)	5 (4%)
Weight decrease	2 (1%)	6 (5%)
Increased creatinine	0	3 (3%)
Cachexia	0	2 (2%)
Red Blood Cell disorders	37 (15%)	28 (21%)
Anemia	33 (13%)	26 (20%)
Urinary system disorders	36 (14%)	22 (17%)
UTI	10 (4%)	6 (5%)
Hematuria	6 (2%)	5 (4%)
Urinary retention	6 (2%)	4 (3%)
Dysuria	5 (2%)	1 (1%)
Vision disorders		
Eye abnormality NOS	5 (2%)	0
White Blood Cell & RES disorders	25 (10%)	21(17%)

F. Adverse Events occurring in > 2% of subjects in either primary or extension treatment phase (cont.)

	Primary (N=293) n (% of enrolled subjects)	Extension Phase (N=168) n (%of enrolled subjects)
Number with at least one adverse event[b,c]	255 (87)	133 (79)
Leukopenia	13 (5%)	7 (5%)
Granulocytopenia	8 (3%)	10 (8%)
Cardiovascular disorders	19 (7%)	12 (9%)
Hypertension	9 (4%)	2 (2%)
Hypotension	5 (2%)	3 (3%)
Cardiac failure	0	3 (3%)
Application Site Reactions	15 (6%)	6 (5%)
Heart rate and rhythm disorders	14 (5%)	5 (4%)
Tachycardia	11 (4%)	4 (3%)
Musculoskeletal system disorders	14 (5%)	14 (8%)
Skeletal pain	5 (2%)	4(2%)
Arthralgia	4 (2%)	5 (4%)
Liver and biliary system disorders	9 (4%)	6 (5%)
Vascular (extracardiac) disorders	7 (3%)	3 (2%)

Modification of sponsor's table 231.33/76, cross referenced with display AE.02B/C and updated with AE.02BB/CB. Percentages recalculated as percentage of persons experiencing an adverse event

[a]Adverse events are coded to body class and preferred term using the WHOART dictionary

[b]Subjects experiencing more than one adverse event within a body class/preferred term is counted once during that body class/preferred term

For the primary treatment period, adverse events emerging after start of study drug administration are included. For those subjects who did not enter the extension period, events occuring within the 3 day therapeutic reach of treatment were included.

G: Adverse events occurring in under 2% of the population during the primary treatment period

Adverse events that occurred in three patients
Gastro-Intestinal system disorders: GI hemorrhage/Oral hemorrhage

Body as a whole disorders: Back pain

Central and peripheral nervous system disorders: Speech disorder

Skin and appendages: Skin disorder

Psychiatric disorders: Paranoia

Metabolic and nutritional disorders: electrolyte abnormality, hyponatremia, hypoproteinemia

White cell and RES disorders: Decreased immunoglobulins

Musculoskeletal system disorders: myalgia

Liver and biliary system disorders: Bilirubinemia, jaundice

Urinary system disorders: abnormal renal function

Adverse events that occurred in two patients
Gastrointestinal system disorders: Dysphagia, Enteritis, Gastritis, Ileus, Sialorrhea, Ulcerative Stomatitis, Toothache, Tooth disorder

Central and peripheral nervous system disorders: hyperasthesia, hypoasthesia, neuralgia, neuropathy, paresthesia, paralysis, stupor

Respiratory system disorders: pulmonary infiltrate

Skin and appendages: skin dryness, skin exfoliation, skin reaction localized

Psychiatric disorders: nervousness

Platelet, bleeding and clotting disorders: coagulation disorder, gingival bleeding, hemorrhage

Red blood cell disorders: pancytopenia

Cardiovascular disorders: cardiac failure, heart murmur, cardiac arrest

G: Adverse events occurring in under 2% of the population during the primary treatment period

Vision disorders: mydriasis, blindness

Musculoskeletal system disorders: pathological fracture

Urinary system disorders: hemorraghic cystitis, micturition disorder, abnormal urine

Adverse events that occurred in one patient
Gastrointestinal system disorders: Anal fissure, Change in bowel habits, Bloody Diarrrhea, Duodenitis, Dyspepsia, Fecal abnormality NOS, Rectal hemorrhage, Intestinal perforation, Acquired megacolon, Esophagitis, Stomatitis, splenomegaly, abnormal hepatic function, elevated SGPT

Body as a whole disorders: allergy drug interaction, drug level increased, injury, multiple organ failure, mouth edema, genital edema, pallor, serum sickness, wound drainage, wound drainage increased, withdrawal syndrome, muscle weakness, wound dehiscence

Central and peripheral nervous system, Psychiatric disorders: ataxia, coma, abnormal CSF, dyskinesia, encephalopathy, hypertensive encephalopathy, hypertonia, hypokinesia, hyporeflexia, migraine, involuntary muscle contractions, peripheral neuropathy, ptosis, vertigo, depersonalization, abnormal dreaming, somnambulism, abnormal thinking

Respiratory system disorders: apnea, aspiration, asthma, bradypnea, decreased breath sounds, bronchospasm, hypoxia, pneumonitis, pneumothorax, pulmonary edema

Skin and appendages: alopecia, bullous eruption, contact dermatitis, eczema, skin depigmentation, urticaria, verruca

Platelet, bleeding and clotting disorders: hematoma, increased prothrombin time

Blood disorders: Abnormal WBC, hemolysis

Metabolic and nutritional disorders: alkalosis, decreased blood urea nitrogen, increased blood urea nitrogen, enzyme abnormality, hypercalcemia, hyperkalemia, generalized edema, periorbital edema

Cardiovascular disorders: circulatory failure, bradycardia

Vision disorders: conjunctival hemorrhage, diplopia, eye infection, eye pain, miosis, photophobia, strabismus

Urinary system disorders: bladder discomfort, cystitis, oliguria, urinary incontinence

H: Adverse events occurring in under 2% of the population during the extension treatment period

Adverse events that occurred in two patients
Gastrointestinal system disorders: Bowel motility disorder, intestinal obstruction

Central and peripheral nervous system disorders: coma

Metabolic and nutritional disorders: hyponatremia, hyperkalemia

Urinary system disorders: cystitis, abnormal renal function

Musculoskeletal system disorders: Skeletal pain

Vision disorders: Conjunctivitis

Adverse events that occurred in one patient
Gastrointestinal system disorders: Enteritis, flatulence, gastroenteritis, intrabdominal hemorrage, hiccup, esophagitis, oral hemorrhage, stomatitis, ulcerative stomatitis toothache/tooth disorder

Body as a whole disorders: Allergy, ascites, fatigue, hyperpyrexia, multiple organ failure, ischemic necrosis, genital edema, serum sickness, withdrawal syndrome

Resistance mechanism disorders: herpes zoster, fungal infection, genital moniliasis

Respiratory system disorders:Apnea, aspiration, atelectasis, bradypnea, decreased breath sounds, bronchospasm, hyperventilation, hypoxia, pleurisy, increased sputum

Psychiatric disorders: delirium, paranoia, paranoid reaction, abnormal thinking, personality disorder

Central and peripheral nervous system disorders: dyskinesia, encephalopathy, intracranial hypertension, hypertonia, hyporeflexia, meningitis neuralgia, neuropathy, paralysis, stupor, vocal cord paralysis, vertigo

Skin and appendages: alopecia, contact dermatitis, erythema, folliculitis, hyperkeratosis, skin disorder, localized skin reaction

Metabolic and nutritional disorders: lactic acidosis, increased blood urea nitrogen, hypoglycemia, hypophosphatemia, increased ldh, increased lipase, generalized edema

Urinary system disorders: oliguria, polyuria, pyuria, urinary incontinence, abnormal urine

H: Adverse events occurring in under 2% of the population during the extension treatment period (cont.)

Platelet, bleeding and clotting disorders: Pulmonary embolism, decreased prothrombin time

Red Blood cell disorders: hemolysis, marrow depression, pancytopenia

White Blood cell and RES disorders: agranulocytosis, leukocytosis, lymphadenopathy

Cardiovascular disorders: Cardiac arrest, cyanosis, circulatory failure /heart murmur

Musculoskeletal system disorders: arthritis, arthropathy, myopathy, pathological fracture

Collagen disorders: Rheumatoid arthritis, GVHD

Vision disorders: abnormal vision

I: Adverse events of special concern by system

The percentages given reflect the percentage of enrolled patients in a given age group

	Total n=293	2-<6 n=66	6-<12 n=100	12-<16 n=117	16-18 n=9
Gastrointestinal disorders					
Vomiting	98 (33%)	24 (36%)	31 (31%)	41 (35%)	2 (22%)
Nausea	69 (24%)	15 (23%)	26 (26%)	27(23%)	1 (11%)
Constipation	38 (13%)	11 (17%)	11(11%)	16 (14%)	0
Respiratory System disorders					
Dyspnea	17 (6%)	3 (5%)	3(3%)	10 (9%)	1(11%)
Respiratory insufficiency	5 (1%)	1 (2%)	3 (3%)	1 (1%)	0
Respiratory depression	7 (3%)	3 (5%)	3(3%)	1(1%)	0
Bradypnea	2 (1%)	0	0	2 (2%)	0
Apnea	2 (1%)	0	1 (1%)	1(1%)	0
Skin disorders					
Pruritis	39 (13%)	12 (18%)	12 (12%)	15 (13%)	0
Application site reaction	19 (6%)	3 (5%)	5 (5%)	11 (9%)	0
Diaphoresis	10 (3%)	2 (3%)	1 (1%)	7 (6%)	0
Psychiatric disorders					
Somnolence	21 (7%)	8	7 (7%)	5	1 (11%)
Agitation	13 (4%)	6	4 (4%)	2(2%)	1(11%)
Nervousness	7 (3%)	1(2%)	1 (1%)	4	1(11%)
Anxiety	12 (4%)	2(3%)	9 (9%)	1 (1%)	0
Insomnia	20 (7%)	2(3%)	7 (7%)	10(9%)	1(11%)
Delirium	1 (1%)	0	1 (1%)	0	0
Paranoid reaction/paranoia	4 (1%)	1(2%)	2 (2%)	1(1%)	0
Hallucinations	7 (3%)	1(2%)	4 (4%)	2(2%)	0
Systemic disorders					
Withdrawal syndrome	2 (1%)	0	0	2(2%)	0

The percentages represent the proportion of patients in a given group
(AE.22CB)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Dawn McNeil
5/19/03 04:06:33 PM
MEDICAL OFFICER

Bob Rappaport
5/19/03 06:44:20 PM
MEDICAL OFFICER
signed for Sharon Hertz, M.D.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-813 / S-036

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA: 19-813	Submission Date(s): 11/25/02
Submission Type; Code	Supplement SE1-036; Supplement to meet the terms of the Pediatric Written Request
Brand Name	Duragesic®
Generic Name	Fentanyl Transdermal System
Primary Reviewer	David Lee
Pharmacometrics Consultant	He Sun
Secondary Reviewer	Suresh Doddapaneni
OCPB Division	DPE 2
ORM division	Division of Anesthetic, Critical Care and Addiction Drug Products
Sponsor	ALZA Corporation
Relevant IND(s)	39,645 and 24,414
Formulation; Strength(s)	25, 50, 75, and 100 µg/hr (12.5 µg/hr used in pediatrics – Approval will be sought through a separate submission)
Proposed Indication	Management of chronic pain in patients who require continuous opioid analgesia for pain that cannot be managed by lesser means such as acetaminophen-opioid combinations, non-steroidal analgesics, or PRN dosing with short-acting opioids
Proposed Dosage Regimen	

1 Executive Summary

ALZA Corporation has submitted a Supplemental NDA in order to present the data for the completeness of dosing information in pediatric population and to fulfill the requirements of the Written Request for Pediatric Studies. The pediatric clinical program was developed to establish safety profile in opioid-tolerant children ages 2 and older, and, to address the need for effective and convenient management of chronic pain in pediatric patients who are opioid tolerant (currently using opioid analgesia) and are in need of opioid analgesia.

Three open-label Phase 3 studies in pediatric patients (FEN-USA-87, FEN-INT-24, and FEN-GBR-14) and a pharmacokinetic study comparing transdermal delivery of fentanyl in adults and children (FEN-FRA-4) were conducted. In addition to the results from these studies, published literature were provided in the submission. Additionally, an analysis of the population pharmacokinetics of Duragesic from studies FEN-USA-87 and FEN-INT-24 was conducted. The clinical trials essential to this NDA were conducted under INDs 39,645 and 24,414.

Fentanyl is an opioid analgesic with a pharmacological action similar to that of morphine. Fentanyl is approximately 75 to 100 times more potent than morphine. Duragesic patch is presumed to provide continuous systemic delivery of fentanyl throughout the recommended

dosing interval of 72 hours. According to the Applicant, Duragesic or Durogesic patch is approved in 64 countries worldwide, and marketed in 57 countries, and between 1991 and 2002, the estimated overall patient exposure for Duragesic systems was more than [redacted] systems (approximately [redacted] per year).

The studies utilized a clinical 12.5 µg/hr dose strength as a starting dose (titration doses used were 25, 50, 75, 100 µg/hr). The Applicant stated that they are not seeking an approval of this strength in this Supplement. Instead they will submit a separate Application for an approval in this strength. Thus, this Supplement does not contain information on Duragesic patch production, manufacturing, testing and controls or non-clinical development. The Applicant stated that all such information remains unchanged as previously provided in NDA 19-813 and supplements to this NDA.

Synopsis of pediatric safety profile from Duragesic patch usage

In the original application, the safety of Duragesic was evaluated in a total of 510 adult patients (n=357 postoperative and n=153 cancer patients). Patients, e.g., postoperative, with acute pain used the patch for 1 to 3 days. For cancer patients, 56% used the patch for more than 30 days, 28% continued treatment for more than 4 months, and 10% used the patch for more than 1 year. The adverse event (AE) profiles in adults included nausea, vomiting, constipation, somnolence, sweating, etc. Hypoventilation was the most serious AE observed (13 (4%) and 3 (2%) in the postoperative and cancer patients, respectively).

According to the current Supplement, the pediatric patients seemed to exhibit similar AEs (e.g., nausea, vomiting, etc.) to that of the adults (the reader should refer to the Medical Officer's Review for a comprehensive safety analysis).

Exposure-response (E-R) relationship

The correlation between occurrences of adverse events (nausea, fever, vomiting, anemia, and abdominal pain) and predicted fentanyl steady-state concentrations from the population PK model was evaluated by logistic regression in the submission. According to the data presented in the Supplement, no significant relationships between AEs and predicted fentanyl steady-state concentrations were observed.

Dose proportionality

Studies FEN-USA-87 and FEN-INT-24 used a dose-titration study design. A dose-normalized fentanyl concentration data (normalized to 12.5 µg/hr) indicated that concentrations from all strengths were similar across time intervals, possibly indicating that there was no accumulation after repeated patch applications. However, due to the variability from the sparse data set, it was not conclusive to observe clear dose proportionality from the studies.

Gender differences

According to a population PK analysis, no gender differences were observed.

Age differences

According to a population PK analysis, age differences were observed.

Body weight differences

According to a population PK analysis, body weight differences were observed for volume of distribution.

Observed steady state fentanyl concentrations (ng/mL) from pediatric patients after repeated application

The pediatric patients enrolled in these studies were between 2 to 16 years. The pediatric patients were arbitrarily grouped[#] as below; however, the first 2-5 year old group can be compared with Study FEN-FRA-4.

Study FEN-USA-87 (normalized to 12.5 µg/hr dose):

	AGE 2 – 5 YEARS[#]	AGE 6 – 10 YEARS[#]	AGE 11 – 16 YEARS[#]
Number of observations	134	250	523
Mean ± SD	**0.47 ± 0.53**	**0.41 ± 0.53**	**0.25 ± 0.37**

Study FEN-INT-24 (normalized to 12.5 µg/hr dose):

	AGE 2 – 5 YEARS[#]	AGE 6 – 10 YEARS[#]	AGE 11 – 16 YEARS[#]
Number of observations	113	81	37
Mean ± SD	**0.55 ± 0.80**	**0.38 ± 0.42**	**0.53 ± 0.68**

Both Studies FEN-USA-87 and FEN-INT-24 (normalized to 12.5 µg/hr dose):

	AGE 2 – 5 YEARS[#]	AGE 6 – 10 YEARS[#]	AGE 11 – 16 YEARS[#]	**ALL**
# of sample observations	247	331	560	1138
Mean ± SD	**0.51 ± 0.66**	**0.40 ± 0.50**	**0.27 ± 0.40**	**0.36 ± 0.51**

Pharmacokinetic parameters in pediatric patients 1.5 – 5 years old (Study FEN-FRA-4)

This study collected a complete fentanyl plasma profile from pediatric and adult patients dosed with a single 72 hour Duragesic patch. The Applicant reported the following PK parameters (n=16 total; n=8 each group):

	DOSE (µg/hr)	Cmax (ng/mL)	Tmax (h)	AUC_{0-144} (ng.h/mL)	$T_{1/2}$ (h)	Vd/f (L)	CL/f (L/hr)
Adults	50	**1.13 ± 0.51**	**33 ± 5.0**	**71 ± 29**	**20.6 ± 5.7**	-	-
Pediatrics	25	**1.70 ± 0.66**	**18 ± 11**	**87 ± 28**	**14.5 ± 6.2**	-	-

The adult controls were between 30 to 65 years.

The Cmax and AUC values for pediatric patients were approx. 50 and 23 % higher, respectively, than that of the adults, even with receiving one-half of the adult's doses. The Tmax value was shorter for the pediatrics.

Additional WinNonLin analysis was conducted for this population and the following PK parameters were generated from the analysis:

	DOSE (µg/hr)	Cmax (ng/mL)	Tmax (h)	AUC_{0-144} (ng.h/mL)	$T_{1/2}$ (h)	Vd/f (L)	CL/f (L/hr)	CL/f/kg (L/hr)
Adults	50	-	-	-	**13.6 ± 6.2**	**1080 ± 597**	**57 ± 21**	**0.76 ± 0.26**
Pediatrics	25	-	-	-	**13.3 ± 5.3**	**420 ± 255**	**21 ± 7.6**	**1.4 ± 0.22**

The estimated $t_{1/2}$ values were comparable between adults and pediatric patients. The values for apparent total CL and Vd for pediatric patients were 59 and 57% lower, respectively, than that of the adult values. When apparent CL was adjusted by body weight, pediatric patients had higher apparent total CL (84% greater) than that of the adults. Additionally, the WinNonLin analysis indicated that apparent Vd and CL are highly correlated (a positive slope), i.e., increase in apparent Vd will give increase in the apparent total CL.

Pediatric population PK analysis

The Applicant submitted estimated apparent total CL values from a population PK analysis using the sparse fentanyl concentration data from studies FEN-USA-87 and FEN-INT-24. The analysis was based on a linear model using the observed steady-state serum fentanly concentration (Css = (Dosing rate) / CL). The following covariates were included in the analysis: time from dosing, study, site, age, weight, height, body surface area (BSA), body mass index (BMI), lean body mass (LBM), gender, race, body temperature, system location, Tanner stage for sexual maturity, dosing gap, and concomitant administration of any medication, a cytochrome P450 3A4 (CYP3A4) inhibitor, or a CYP3A4 inducer. The final model included clinical site and body surface area (BSA): $CL = \exp(-\beta_0 - \beta_{2\_Site} - \beta_3 * BSA)$

The estimated apparent total CL and body weight adjusted apparent total CL from this analysis were 28.1 ± 15.3 L/h and 0.92 ± 0.51 L/h/kg, respectively.

Structure model and parameter estimates from WinNonLin analysis (Study FEN-FRA-4) were used in Nonmem population PK analysis. The sparse data from studies FEN-USA-87 and FEN-INT-24 were analyzed with age, body weight, and BSA as covariates. The final model indicated that body weight was correlated with Vd and the degree of correlation due to age or BSA was similar on apparent CL. However, BSA as a covariate produced more robust curve fitting. Thus, if needed, the dosage adjustment based on BSA is preferred based on the analysis.

Based on Nonmem analysis' post hoc predictions, the following individual PK parameters were obtained (mean ± SD):

	AGE 2 – 5 YEARS[1]	AGE 6 – 10 YEARS[1]	AGE 11 – 16 YEARS[1]	ALL
Number of subjects	56	75	142	273
CL/f (L/h)	19.5 ± 2.4	23.8 ± 3.2	29.5 ± 4.9	25.9 ± 5.7
CL/f/kg (L/h/kg)	1.26 ± 0.20	0.92 ± 0.21	0.66 ± 0.17	0.85 ± 0.3
Vd/f (L)	200 ± 45	336 ± 119	547 ± 200	418 ± 213
Vd/f/kg (L/kg)	12.7 ± 0.5	12.0 ± 1.2	11.3 ± 0.75	11.8 ± 1.0

1: Arbitrary age grouping; however, the first 2-5 year old group can be compared with Study FEN-FRA-4.

Thus, overall comparison for the apparent CL is as follows:

	CL/f (L/hr)	**CL/f/kg (L/hr/kg)**
Applicant's adult data[1]	-	**0.77 ± 0.30**
Applicant's ped. pop. PK analysis (all subjects)	**28.1 ± 15.3**	**0.92 ± 0.51**
Study FEN-FRA-4 WinNonLin analysis[2]	**21 ± 7.6**	**1.4 ± 0.22**
Nonmem ped. pop. PK analysis (all subjects)	25.9 ± 5.7	0.85 ± 0.3

1: Population analysis from Studies FEN-GBR-3 and FEN-GBR-4; the adult clearance data were discussed in the Supplement; the actual adult data were not submitted.
2: Age group: 1.5 – 5 years old

The apparent CL values across all analysis were comparable. Looking at the numbers more closely, the Applicant's apparent total CL value was comparable to that of the pediatric 6 – 10 year old age group. It is noticeable that the apparent CL for the youngest group (2-5 year olds) is 64% larger than that of the adults. Furthermore, Nonmem analysis indicated that apparent CL for pediatric patients begins to differ than the adults at 9 years of age (based on 20% difference in mean adult apparent clearance using 0.77 ± 0.3 L/hr/kg as reference; range 0.62 – 0.92 L/h/kg). Therefore, if necessary, based on the fentanyl apparent clearance, pediatric patients less than 9 years old should be dose adjusted accordingly.

Additionally, the following steady state fentanyl concentrations were calculated using the mean apparent CL obtained from Nonmem analysis for each age group and compared with the

observed concentrations from Studies FEN-USA-87 and FEN-INT-24 (normalized to 12.5 µg/hr dose):

	AGE 2 – 5 YEARS[1]	AGE 6 – 10 YEARS[1]	AGE 11 – 16 YEARS[1]	ALL
Estimated steady state fentanyl conc. (ng/mL)[2]	0.64	0.53	0.42	0.48
Observed steady state fentanyl conc. (ng/mL)	**0.51 ± 0.66**	**0.40 ± 0.50**	**0.27 ± 0.40**	**0.36 ± 0.51**

1: Arbitrary age grouping; however, the first 2-5 year old group can be compared with Study FEN-FRA-4
2. Css = (Dosing rate) / CL/f ; dosing rate is 12.5 µg/hr.

1.1 Recommendation

The Office of Clinical Pharmacology and Biopharmaceutics / Division of Pharmaceutical Evaluation II (OCPB/DPE-II) has reviewed Supplement SE1-036 to NDA 19-813 submitted on November 25, 2002.

The information contained in the Supplemental NDA is acceptable. However, the proposed labeling should be communicated to the Applicant.

1.2 Comment to the Applicant

Proposed by the Applicant:

[ ]

2 Table of Contents

3 Summary of CPB Findings

FEN-USA-87 Study

This trial was a single-arm, multi-center, nonrandomized, open-label, dose titration, safety and population PK analysis trial in pediatric patients with malignant or nonmalignant diseases. The dose strengths used were 12.5 (starting dose), 25, 50, 75 and 100 µg/hr. The Duragesic patch was applied every 72 hours for 15 days. Serum fentanyl concentrations were also measured on Days 1, 2, 4, 7 and 16. Five blood samples per subject were drawn during the primary treatment period to determine fentanyl serum concentrations during the trial. The volume of blood to be collected with each sample was 2 mL. The limit of quantification (BLQ) concentration was ng/mL. A total Number of pediatric subjects enrolled was 199:

	Age 2 – < 6	6 – <12	12 – <16
N	27	67	102

a) No PK parameters were computed from the study due to the fact that the data collection plan focused on concentrations toward the end of the dosing intervals. However, the following steady state fentanyl concentrations were reported *(normalized to 12.5 µg/hr dose):*

	AGE 2 – 5 YEARS#	AGE 6 – 10 YEARS#	AGE 11 – 16 YEARS#
Number of observations	134	250	523
Mean ± SD	0.47 ± 0.53	0.41 ± 0.53	0.25 ± 0.37

#: Arbitrary age grouping; however, the first 2-5 year old group can be compared with Study FEN-FRA-4

b) The profiles hinted that steady state was reached at approximately 24 hours post the first patch application. A large variability in concentration was observed within and between subjects and a substantial overlap in concentrations across all dose levels was observed.

c) After the normalization, the majority of individual subject fentanyl profiles were relatively flat (on average, normalized fentanyl concentrations from all strengths were similar across time intervals following application of the first patch, as well as subsequent patches), possibly indicating that there were no accumulation after repeated patch applications. Additionally, due to the variability from the sparse data set, it was not conclusive to observe clear dose proportionality in this study.
d) The Applicant stated that younger subjects were generally titrated to lower fentanyl doses than were older subjects, which is an expected finding in a population wherein weight is correlated with age. For example, all subjects >5 years of age were treated with doses ranging between 12.5 and 62.5 µg/hour, whereas older subjects received doses as high as 250 µg/hour. For similar reasons, subjects of smaller body size generally received lower fentanyl doses. Nausea, fever, and vomiting were the most common AEs.
e) A population PK analysis was performed on the pooled data from this study and the FEN-LNT-24 study; the results were reported in a separate stand-alone population PK report.

FEN-INT-24 Study

This was a single-arm, non-randomized, open-label, 15-day (patches were to be replaced every 72 hours) multi-center trial to determine the safety, clinical utility and PK of Duragesic patch in pediatric patients with continuous pain requiring opioid therapy for at least the duration of the trial. All subjects started treatment with a 12.5 µg/h patch. Trial medication was provided as 12.5, 25, 50, 75, and 100 µg/h patches. Five blood samples (serum fentanyl concentrations) were collected during the trial (Days 1, 2, 4,7 or 10, and 13 or 16; 2 mL each). The limit of quantification (BLQ) concentration was 0.1 ng/mL. A total number of pediatric subjects enrolled were 53:

	Age 2 – 6	Age 7 – 12
N	29	24

a) No PK parameters were computed from the study due to the fact that the data collection plan focused on concentrations toward the end of the dosing intervals. However, the , the following steady state fentanyl concentrations were reported (normalized to 12.5 µg/hr dose):

	AGE 2 – 5 YEARS#	AGE 6 – 10 YEARS#	AGE 11 – 16 YEARS#
Number of observations	113	81	37
Mean ± SD	0.55 ± 0.80	0.38 ± 0.42	0.53 ± 0.68

#: Arbitrary age grouping; however, the first 2-5 year old group can be compared with Study FEN-FRA-4

b) The profiles hinted that steady state was reached at approximately 24 hours post the first patch application. A large variability in concentration was observed within and between subjects and a substantial overlap in concentrations across all dose levels was observed.
c) After the normalization, the majority of individual subject fentanyl profiles were relatively flat (on average, normalized fentanyl concentrations from all strengths were similar across time intervals following application of the first patch, as well as subsequent patches), possibly indicating that there were no accumulation after repeated patch applications. Additionally, due to the variability from the sparse data set, it was not conclusive to observe clear dose proportionality in this study.
d) Nausea, fever, and vomiting were the most common AEs.
e) A population PK analysis was performed on the pooled data from this study and the Study FEN-USA-87; the results were reported in a separate stand-alone population PK report.

FEN-GBR-14 Study

This was an open label study comprising of 3 phases: a pre-dose, a Durogesic treatment and a follow-up phase. The treatment phase lasted for 15 days (every 72 hour patch application).

Duragesic was titrated in steps of 25 µg/hr to achieve adequate pain control. Plasma concentrations were to be reported. Twenty-six subjects completed the 15-day treatment phase, 23 entered the follow-up phase and 3 subjects completed as least 12 weeks of follow-up. The median age of subjects was 10.5 years (range 2.6 – 18.8 years). Of subjects participating, 30/41 (73%) was male and 11/41 (27%) was female. The median body weight was 32 kg (range 11.0-68.8 kg) and the median height was 139.15 cm (range 79.6 – 181.0 cm). Of participating subjects, 36/41 (88%) had pain caused by a malignancy; 5/31 (12%) subjects had pain due to other causes.

The Applicant stated that due to the limited number of PK samples obtained and the lack of post-treatment samples, PK analyses were not performed.

FEN-FRA-4 Study

This was an open-label, multi-center, single-arm, nonrandomized study in 8 pediatric (1.5 – 5 years old) and 8 adults (30 – 65 years old) patients. Subjects were hospitalized for abdominal surgery lasting at least 3 hours. Patch was applied 2 hours prior to anesthesia induction and left in place for 72 hours. Blood samples were taken during the 72 hours of patch use and 72 hours after patch removal. Patch strengths were 25 and 50 µg/hr for pediatric and adults, respectively.

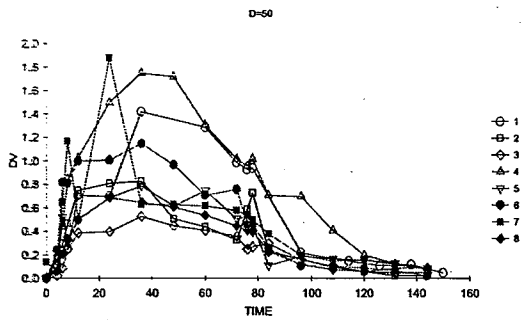
The Applicant reported that, in pediatric patients, Tmax was shorter (14.5 hours vs. 21 hours, pediatric vs. adults, respectively) and plasma concentrations were higher. No apparent plateau of plasma concentrations was observed in 6 of the 8 pediatric patients. After patch removal, the apparent t1/2 was shorter in pediatric patients than that of adults (14.5 ± 6.2 vs. 20.6 ± 5.7 hours), although the difference was not statistically significant:

	DOSE (µg/hr)	Cmax (ng/mL)	Tmax (h)	AUC_{0-144} (ng.h/mL)	$T_{1/2}$ (h)	Vd/f (L)	CL/f (L/hr)
Adults	50	**1.13 ± 0.51**	**33 ± 5.0**	**71 ± 29**	**20.6 ± 5.7**	-	-
Pediatrics	25	**1.70 ± 0.66**	**18 ± 11**	**87 ± 28**	**14.5 ± 6.2**	-	-

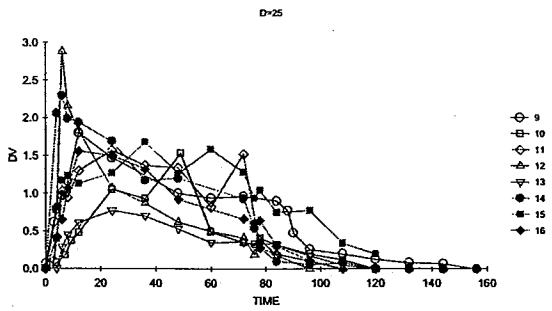
The adult controls were between 30 to 65 years.

Dr. He Sun (Pharmacometrics node) and this reviewer conducted further analysis (WinNonLin). The plasma concentration profiles (see below profiles) from all adult and pediatric patients were individually fitted by WinNonLin program (See appendix A). The model used was a percutaneous model with 3 compartments. The following profiles and table was generated from WinNonLin analysis.

Adult patients (Study 04; 50 µg/hr strength):



Pediatric patients (Study 04; 25 µg/hr strength)



WinNonlin individual subject parameters:

ID	Group	V1 (L)	V2 (L)	CL (L/h)	Q	DINF (µg)	TFST (h)	TINF (h)	THALF (h)	WT (kg)	CLwt (L/h/kg)
1	ADULT	924.3	296.97	36.44	0.55	1325.73	57.49	76.65	17.58	70	0.52
2	ADULT	705.58	114.69	68.02	1.66	2750.56	34.3	78.19	7.19	79	0.86
3	ADULT	1553.87	150.68	95.47	2.65	1991.61	53.37	89.96	11.28	85	1.12
4	ADULT	727.78	135.35	27.15	1.59	1419.59	41.87	81.71	18.58	84	0.32
5	ADULT	1140.73	72.5	64.82	0.85	2662.74	33.67	72.88	12.2	85	0.76
6	ADULT	321.76	398.78	47.32	4.96	2014.18	53.45	78.93	4.71	56	0.84
7	ADULT	1001.08	308.35	50.52	0.5	1699.46	22.59	76.81	13.73	75	0.67
8	ADULT	2263.31	464.44	66.52	0.2	349.22	41.21	166.7	23.58	66	1.01
9	CHILDREN	215.49	234.77	15.74	1.61	1293.36	16	83.41	9.49	14.5	1.09
10	CHILDREN	594.16	221.5	27.14	1.21	218.12	48.99	100.89	15.17	18	1.51
11	CHILDREN	168.1	201.77	18.21	0.38	1467.03	31.78	72.1	6.4	13	1.4
12	CHILDREN	509.98	166.13	23.24	0.23	504.64	6	67.18	15.21	13.5	1.72
13	CHILDREN	919.72	132.65	36.3	0.45	827.02	22.52	81.63	17.56	22	1.65
14	CHILDREN	197.49	212.82	15.72	0.09	1316.63	2.08	65.62	8.71	12	1.31
15	CHILDREN	436.01	236.9	13.44	0.05	1395.26	7.2	64.24	22.48	11	1.22
16	CHILDREN	317.89	193.7	19.16	0.13	1121.49	17.38	68.41	11.5	15	1.28

Mean values: Adults

	V1 (L)	V2 (L)	CL (L/hr)	Q	DINF	TFAST	TINF
Mean	1080	243	57	1.6	1776	42	90
Median	963	224	58	1.2	1845	42	79
SD	597	144	21	1.6	775	12	31

Mean values: Pediatrics

	V1 (L)	V2 (L)	CL (L/hr)	Q	DINF	TFAST	TINF
Mean	420	200	21	0.52	1018	19	75
Median	377	207	19	0.30	1207	17	70
SD	255	36	7.6	0.58	457	15	13

V1: Apparent central Vd
V2: Apparent peripheral Vd
CL: Apparent CL
Q : Inter-compartment clearance (K21*V2/K12/V1)
Dinf: Predicted 'slow infusion dose
Tfast: Predicted 'fast' infusion time – set as time to reach steady-state plasma concentration
Tinf: Predicted 'slow' infusion time – set as total patch application duration (72 hours)

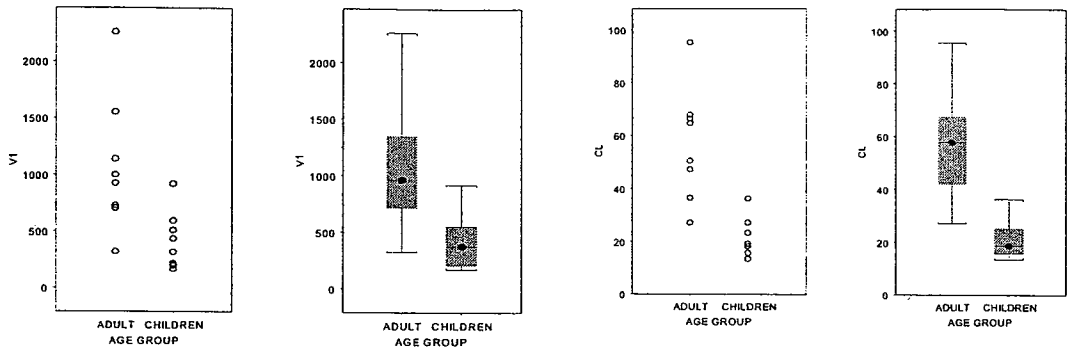
$T_{1/2}$ (hr) comparison:

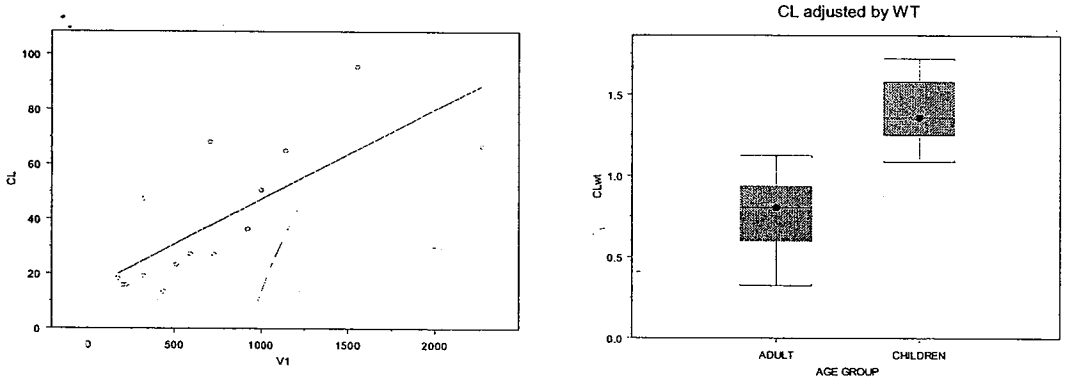
	Adult	Pediatrics
Mean ± SD	13.6 ± 6.2	13.3 ± 5.3

Weight adjusted CL : CLwt (L/hr) comparison:

	Adult	Pediatrics
Mean± SD	0.76 ± 0.26	1.40 ± 0.22

Relationships between various parameters plotted as box diagrams:





This study indicated that there was a correlation between apparent CL and Vd. When apparent CL was adjusted by body weight, pediatric patients had higher values than that of the adults.

In conclusion the following PK parameters were compiled from the analysis:

	DOSE (µg/hr)	Cmax (ng/mL)	Tmax (h)	AUC_{0-144} (ng.h/mL)	$T_{1/2}$ (h)	Vd/f (L)	CL/f (L/hr)	CL/f/kg (L/hr)
Adults	50	-	-	-	**13.6 ± 6.2**	**1080 ± 597**	**57 ± 21**	**0.76 ± 0.26**
Pediatrics	25	-	-	-	**13.3 ± 5.3**	**420 ± 255**	**21 ± 7.6**	**1.4 ± 0.22**

The estimated $t_{1/2}$ values were comparable between adults and pediatric patients. The values for apparent total CL and Vd for pediatric patients were 59 and 57% lower, respectively, than that of the adult values. When apparent CL was adjusted by body weight, pediatric patients had higher apparent total CL (84% greater) than that of the adults. Additionally, the WinNonLin analysis indicated that apparent Vd and CL are highly correlated (a positive slope), i.e., increase in apparent Vd will give increase in the apparent total CL.

Nonmem analysis

The model initial specifications were further utilized in Nonmem analysis to obtain the population parameters (e.g., CL/f, Vd/f, etc.) from the sparse data set from studies FEN-INT-24 and FEN-USA-87. The sparse data from studies FEN-USA-87 and FEN-INT-24 were analyzed with age, wt, and BSA as covariates. The final model indicated that body weight was correlated with Vd.

Structure model and parameter estimates from WinNonLin analysis (Study FEN-FRA-4) were used in Nonmem population PK analysis. The sparse data from studies FEN-USA-87 and FEN-INT-24 were analyzed with age, body weight, and BSA as covariates. The final model indicated that body weight was correlated with Vd and the degree of correlation due to age or BSA was similar on apparent CL. However, BSA as a covariate produced more robust curve fitting. Thus, if needed, the dosage adjustment based on BSA is preferred based on the analysis.

The following relationships were obtained from the analysis:

$$Vd/f = 36.2 + 10.4*wt$$
$$CL/f = 10.8 + 13.5*BSA$$

Based on Nonmem analysis' post hoc predictions, the following individual PK parameters were obtained (mean ± SD):

	AGE 2 – 5 YEARS[1]	AGE 6 – 10 YEARS[1]	AGE 11 – 16 YEARS[1]	ALL
Number of subjects	56	75	142	273
CL/f (L/h)	19.5 ± 2.4	23.8 ± 3.2	29.5 ± 4.9	25.9 ± 5.7
CL/f/kg (L/h/kg)	1.26 ± 0.20	0.92 ± 0.21	0.66 ± 0.17	0.85 ± 0.3
Vd/f (L)	200 ± 45	336 ± 119	547 ± 200	418 ± 213
Vd/f/kg (L/kg)	12.7 ± 0.5	12.0 ± 1.2	11.3 ± 0.75	11.8 ± 1.0

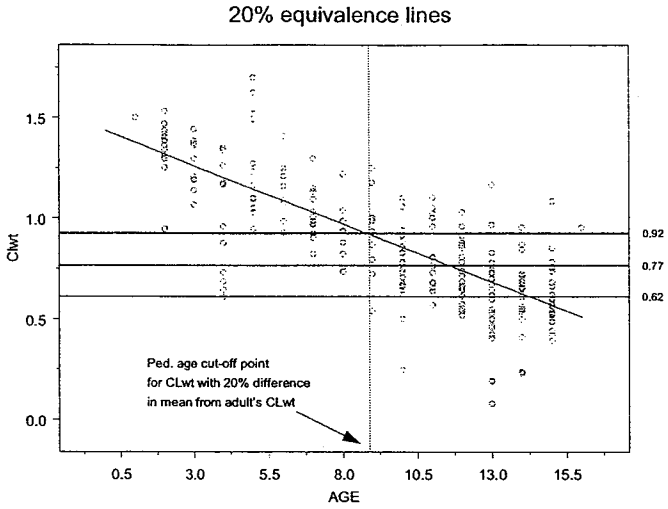
1: Arbitrary age grouping; however, the first 2-5 year old group can be compared with Study FEN-FRA-4.

Thus, overall comparison for the apparent CL is as follows:

	CL/f (L/hr)	**CL/f/kg (L/hr/kg)**
Applicant's adult data[1]	-	**0.77 ± 0.30**
Applicant's pop. PK analysis	**28.1 ± 15.3**	**0.92 ± 0.51**
FEN-FRA-4 WinNonLin analysis	**21 ± 7.6**	**1.4 ± 0.22**
Nonmem pop. PK analysis (all subjects)	25.9 ± 5.7	0.85 ± 0.3

1: Population analysis from Studies FEN-GBR-3 and FEN-GBR-4; the adult clearance data were discussed in the Supplement; the actual adult data were not submitted.

The apparent CL values across all analysis were comparable. However, the Applicant's apparent total CL value was comparable to that of the pediatric 6 – 10 year old age group. It is noticeable that the apparent CL for the youngest group (2-5 year olds) is 64% larger than that of the adults. Furthermore, Nonmem analysis indicated that apparent CL for pediatric patients begins to differ than the adults at 9 years of age (based on 20% difference in mean adult apparent clearance using 0.77 ± 0.3 L/hr/kg as reference; range ——— g). Therefore, if necessary, based on the fentanyl apparent clearance, pediatric patients less than 9 years old should be dose adjusted accordingly.



Finally, the following steady state fentanyl concentrations were calculated using the mean apparent CL obtained from Nonmem analysis for each age group and compared with the observed concentrations from Studies FEN-USA-87 and FEN-INT-24 (normalized to 12.5 µg/hr dose):

	AGE 2 – 5 YEARS[1]	AGE 6 – 10 YEARS[1]	AGE 11 – 16 YEARS[1]	ALL
Estimated steady state fentanyl conc. (ng/mL)[2]	0.64	0.53	0.42	0.48
Observed steady state fentanyl conc. (ng/mL)	**0.51 ± 0.66**	**0.40 ± 0.50**	**0.27 ± 0.40**	**0.36 ± 0.51**

1: Arbitrary age grouping; however, the first 2-5 year old group can be compared with Study FEN-FRA-4

2. Css = (Dosing rate) / CL/f ; dosing rate is 12.5 µg/hr.

Applicant's Pop PK analysis of Studies FEN-INT-24 and FEN-USA-87

Data characterizing the population PK of fentanyl after transdermal administration (Duragesic) in pediatric subjects were derived from two studies, FEN-INT-24 and FEN-USA-87 using linear mixed-effects modeling (Proc Mixed in SAS for Windows, Version 8.1). The 242 subjects provided 886 evaluable serum concentrations, including 188 concentrations from 50 subjects in FEN-INT-24 and 698 concentrations from 192 subjects in FEN-USA-87. The following covariates were included in the analysis: time from dosing, study, site, age, weight, height, body surface area (BSA), body mass index (BMI), lean body mass (LBM), gender, race, body temperature, system location, Tanner stage for sexual maturity, dosing gap, and concomitant administration of any medication, a cytochrome P450 3A4 (CYP3A4) inhibitor, or a CYP3A4 inducer.

The following definitions were used for BSA, LBM, and BMI.

- **Body surface area (BSA) using the method of Haycock :**

$$BSA(m^2) = 0.024265 * Weight(kg)^{0.5378} * Height(cm)^{0.3964}$$

- Lean body mass (LBM) using the method of James :

$$LBM(kg) = 1.10 * Weight(kg) - 128 * \left(\frac{Weight(kg)}{Height(cm)}\right)^2 \text{ for males}$$

$$LBM(kg) = 1.07 * Weight(kg) - 148 * \left(\frac{Weight(kg)}{Height(cm)}\right)^2 \text{ for females}$$

- Body mass index (BMI) using the method of Stevens

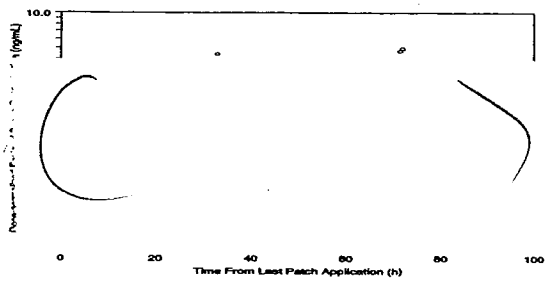
$$BMI = \frac{Weight(kg)}{[Height(cm)]^2}$$

The basic model (equation below) was based on the steady-state serum fentanly concentration, where CL is the apparent clearance. This is a linear model with no intercept and slope equal to CL^{-1} :

$$C_{ss} = \left(\frac{Dosing}{Rate}\right) * \frac{1}{CL}$$

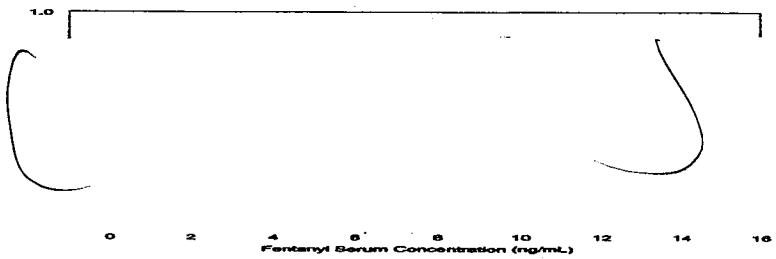
In this model, the distribution of serum fentanyl concentrations was assumed to be log-normal:

Dose-Normalized Serum Fentanyl Concentration-Time Profile



Note: The solid line is a locally weighted smoother with 0.5 span, equal weights, and linear model.

Distribution of Serum Fentanyl Concentrations



The final model for fentanyl at steady state included clinical site and body surface area (BSA):

$$Ln(C_{ij}) = \beta_0 + \beta_1 * Ln\left(\frac{Dosing}{Rate}\right) + \beta_{2\_Site} + \beta_3 * BSA + e_{ij}$$

Finally, empirical Bayes estimates of fentanyl apparent clearance and steady-state concentration were calculated from the following equations:

$$CL = \exp\left(-\beta_0 - \beta_{2\_Site} - \beta_3 * BSA\right)$$

and

$$C_{ss} = \left(\frac{Dosing}{Rate}\right) * \frac{1}{CL}$$

The following results were reported from the Applicant's population PK analysis:

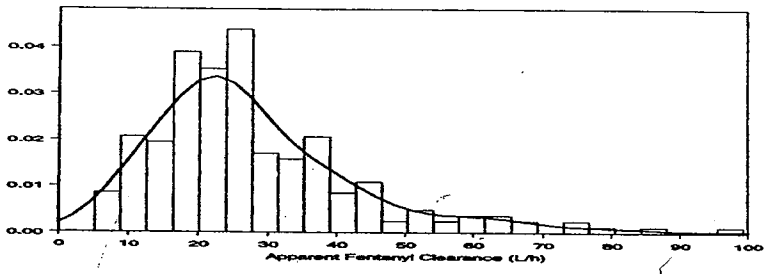
a) Calculated and distribution of apparent CL (L/h)

Distribution of CL (L/h) Across BSA Quartiles

BSA quartile	n	Statistics Mean ± SD	CV%	Median	Range
1st Quartile (<0.8 m^2)	50	20.09 ± 8.59	42.8	18.57	5.09 – 43.71
2nd Quartile (0.8-1.1 m^2)	56	25.49 ± 11.43	44.9	24.40	5.29 – 52.65
3rd Quartile (1.1-1.4 m^2)	56	29.25 ± 13.86	47.4	25.84	7.03 – 73.01
4th Quartile (>1.4 m^2)	56	36.72 ± 19.88	54.1	29.49	9.76 – 99.33
All Quartiles	218	28.10 ± 15.32	54.5	24.48	5.09 – 99.33

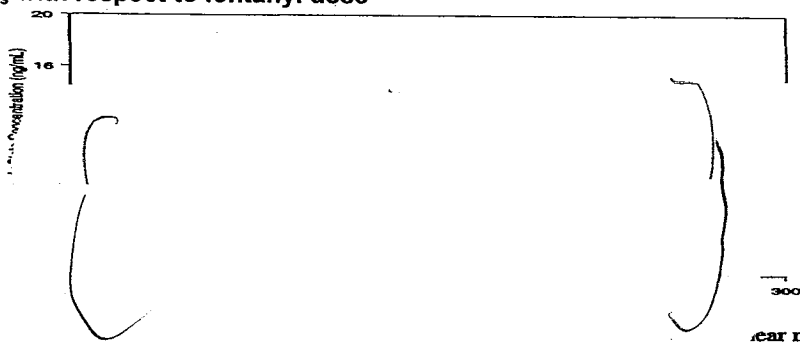
(Cross-Reference: Section 8, Attachment 4.1)

Distribution of Apparent Fentanyl Clearance Estimated from the Final Model



b) Steady-state concentrations and apparent clearance (CL) were dependent upon BSA and study site. The effect of BSA was the most pronounced of all body size—related covariates. An increase in BSA of 0.1 in^2 is predicted to result in a 4.8% increase in CL and a 4.6% decrease in steady-state concentration.

Estimated C_{ss} with respect to fentanyl dose



N
((ear model.

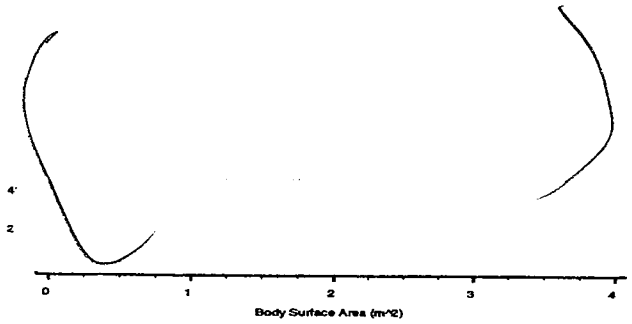
c) Adult subject values were derived from population analysis of data from studies FEN-GBR-3 and FEN-GBR-4 in adult subjects. The reported body weight adjusted total clearance for adults is 0.77±0.30 L/h/kg. The Applicant did not specify whether this value is an apparent clearance.

d) When clearance values were adjusted for body weight, the clearance values were 20% higher in the pediatric group (0.92±0.51 L/h/kg in pediatric subjects vs. 0.77±0.30 L/h/kg in adults).

e) Since BSA had the most pronounced effect on fentanyl clearance, the correlation between these two parameters was examined for the pediatric and adult data together (Figure 11). As seen in this figure, the regression line for the two populations overlaps, indicating BSA to be

the most relevant parameter for comparing fentanyl pharmacokinetics in adult and pediatric subjects. Fentanyl clearance values adjusted to BSA appear to be similar in adults and pediatric subjects: 19.0 ± 7.0 and 26.0 ± 13 L/h/m2, respectively.

Relationship between Clearance (L/h) and Body Surface Area (m^2)



4 QBR

4.1 General Attributes

What is the pharmacological class for fentanyl?

Fentanyl is an opioid analgesic with a pharmacologic action similar to that of morphine but with 75 to 100 times greater potency.

4.2 General Clinical Pharmacology

Is there any exposure-response relationship information for combination tablet?

The correlation between occurrences of AEs such as nausea, fever, vomiting, anemia, and abdominal pain and predicted fentanyl steady-state concentrations from the population PK model was evaluated by logistic regression in the submission. According to the data presented, no significant relationships between AEs and predicted fentanly steady-state concentrations were observed.

Does the patch show accumulation after multiple dosing?

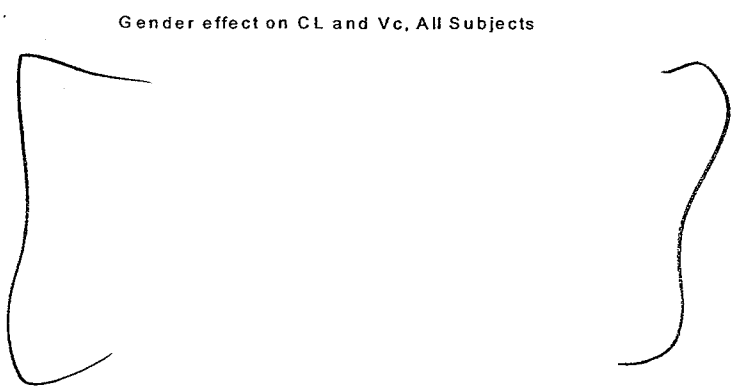
Studies FEN-USA-87 and FEN-INT-24 used a dose-titration study design. A dose-normalized fentanyl concentration data (normalized to 12.5 µg/hr) indicated that concentrations from all strengths were similar across time intervals, possibly indicating that there was no accumulation after repeated patch applications. However, due to the variability from the sparse data set, it was not conclusive to observe clear dose proportionality from the studies.

Note that the Applicant is not seeking approval of the 12.5 µg/hr dose strength at this time.

4.3 Intrinsic Factors

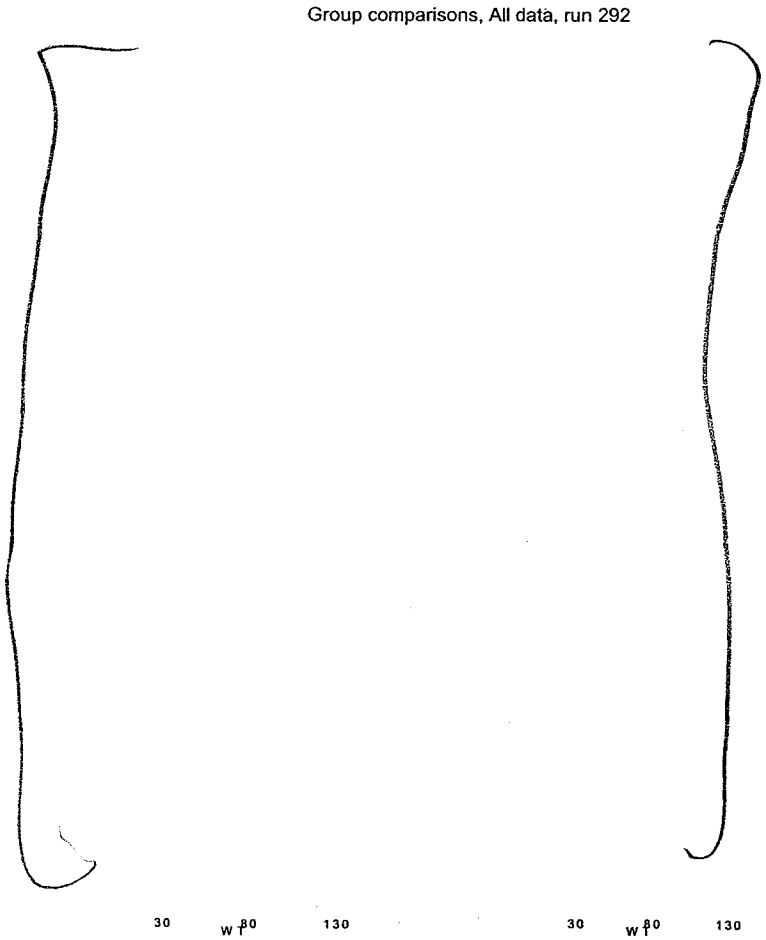
Are there any gender differences observed?

No significant differences between pediatric males and females were observed (WinNonLin and NonMem print out).



Are there any age or weight differences observed?

Effects of age on the pharmacokinetics, CL/f and Vd/f, of fentanyl were observed (Nonmem). The following box diagram showed that both CL/f and Vd/f decreased with decrease in age.



The covariates, BSA, age and wt, were correlated with Vd/f or CL/f. (Nonmem output).

4.4 General Biopharmaceutics

Is an approval of 12.5 µg/hr patch pursued in the Supplement?

No, an approval of 12.5 µg/hr patch is not requested in the Supplement. The Applicant will be submitting a separate submission to pursue the 12.5 µg/hr patch.

4.5 Analytical

Were the analytical procedures used to determine drug concentrations in this NDA acceptable?

Yes, fentanyl was analyzed by the validated radioimmunoassay method. The limit of quantitation was

5 Labeling

The Applicant's proposed labeling contain a modest revision under the Clinical Pharmacology section (e.g., clearance). A review of the proposed labeling is as follows:
Proposed by the Applicant:

[ ]

38 Page(s) Withheld

_____ Trade Secret / Confidential

X Draft Labeling

_____ Deliberative Process

Withheld Track Number: Clin Pharm/Bio- 1a

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

David Lee
5/14/03 11:11:38 AM
BIOPHARMACEUTICS
Review includes Agency's WinNonlin (FEN-FRA-04) and Nonmem (FEN-USA-87 and FEN-INT-24) analyses.

He Sun
5/14/03 11:50:40 AM
PHARMACOLOGIST

Suresh Doddapaneni
5/14/03 11:54:18 AM
BIOPHARMACEUTICS

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-813 / S-036

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

SECTION 13: PATENT DECLARATION

The undersigned declares that the following patents cover the formulation, composition, and/or method of use of DURAGESIC® (fentanyl transdermal system). This product is the subject of this application for which approval is being sought.

PATENT NO.	TYPE	EXPIRATION	PATENT OWNER
4588580	Formulation and Method of Use	July 23, 2004	ALZA Corporation

Marc R Benson Nov. 1, 2002

Name: Marc R. Benson Date
Title: Assistant Secretary,
ALZA Corporation

Exclusivity Checklist

NDA: 19-813/S-036				
Trade Name: Duragesic®				
Generic Name: Fentanyl Transdermal System				
Applicant Name: Alza Corporation				
Division: DACCADP (HFD-170)				
Project Manager: Kim Compton				
Approval Date:5/20/03				
PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?				
1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.				
a. Is it an original NDA?	Yes		No	X
b. Is it an effectiveness supplement?	Yes	X	No	
c. If yes, what type? (SE1, SE2, etc.)	**SE1**			
Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")	Yes	X	No	
If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.				
Explanation:				
If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:				
Explanation:				
d. Did the applicant request exclusivity?	Yes	X	No	
If the answer to (d) is "yes," how many years of exclusivity did the applicant request?	Pediatric Exclusivity of 6 months was requested and granted.			
IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS.				
2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use?	Yes		No	X
If yes, NDA #				
Drug Name:				
IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS.				
3. Is this drug product or indication a DESI upgrade?	Yes		No	X
IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS (even if a study was required for the upgrade).				
PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES				
(Answer either #1 or #2, as appropriate)				
1. Single active ingredient product.	Yes	X	No	
Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such	Yes	X	No	

as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.				
If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).				
Drug Product Actiq, Oralet				
NDA 20-747, NDA 20-195				
2. Combination product.	Yes		No	X
If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)	Yes		No	
If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).				
IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS. IF "YES," GO TO PART III.				
PART III: THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS				
To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."				
1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.	Yes	X	No	
IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS.				
2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application. For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.				
a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?	Yes	X	No	
If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCKS.				
Basis for conclusion:				
b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application? ***NOTE: According to the Medical Officer, we informed the applicant that none of the published studies would be able to support approval and that they would need to perform additional studies.***	Yes		No	X
1) If the answer to 2 b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.	Yes		No	X
If yes, explain:				

2) If the answer to 2 b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?	Yes		No	X
If yes, explain:				
c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:				
FEN-USA-87	I 39, 645			
FEN-INT-24				
FEN-FRA-4				
FEN-GBR-14				
3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.				
a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")				
	Yes		No	X
If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:				
b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?				
	Yes		No	X
If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:				
If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"): All listed studies are new.				
4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.				
a. For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor? **Yes**				
b. For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study? **N/A (all studies listed carried out under applicant's IND/or with applicant as the sponsor).**				
c. Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)	Yes		No	X
If yes, explain:				

Completed by: Kim Compton, Regulatory Project Manager (with the assistance of Elizabeth McNeil, M.D., Medical Officer) 5/20/03

Concurred by: Bob Rappaport, M.D. Acting Director 5-20-03

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Kimberly Compton
5/20/03 06:13:24 PM

PEDIATRIC EXCLUSIVITY DETERMINATION CHECKLIST

PART I - TO BE COMPLETED BY THE REVIEWING DIVISION.

Date of Written Request from FDA 2/27/01 (orig = 7/15/99, amend #1 = 11/30/99, amend #2 = 2/27/01). Application Written Request was made to: NDA/(IND#)

Timeframe Noted in Written Request for Submission of Studies 12/1/02 (from amend #2)

NDA# 19-813 Supplement # S-036 Choose one: SE1 SE2 SE3 SE4 SE5 SE6 SE7 SE8 SLR

Sponsor Alza Corporation

Generic Name Fentanyl Trade Name Duragesic

Strength 25, 50, 75 or 100mcg/hr. Dosage Form/Route Transdermal System

Date of Submission of Reports of Studies 11/25/02

Pediatric Exclusivity Determination Due Date (60 or 90 days from date of submission of studies) 2/25/03

Was a formal Written Request made for the pediatric studies submitted?	Y ✓	N ___
Were the studies submitted after the Written Request?	Y ✓	N ___
Were the reports submitted as a supplement, amendment to an NDA, or NDA?	Y ✓	N ___
Was the timeframe noted in the Written Request for submission of studies met?	Y ✓	N ___
If there was a written agreement, were the studies conducted according to the written agreement? OR If there was no written agreement, were the studies conducted in accord with good scientific principles?	Y ✓	N ___
Did the studies fairly respond to the Written Request?	Y ✓	N ___

SIGNED Elizabeth Mason (Reviewing Medical Officer) DATE 1/23/03

Do not enter in DFS - FORWARD TO PEDIATRIC EXCLUSIVITY BOARD, HFD-960.

PART II - TO BE COMPLETED BY THE PEDIATRIC EXCLUSIVITY BOARD

Pediatric Exclusivity ✓ **Granted** ___ **Denied**

Existing Patent or Exclusivity Protection:

NDA/Product #	Eligible Patents/Exclusivity	Current Expiration Date
NDA 19-813	4588580	07/23/04

SIGNED _____ DATE 1/29/03

Revised: 11/30/2001

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/s/

Grace Carmouze
1/29/03 04:31:57 PM

PEDIATRIC PAGE

(Complete for all APPROVED original applications and efficacy supplements)

NDA # 19-813 Supplement Type (e.g. SE5):SE1 Supplement Number: 036

Stamp Date: November 26, 2002 Action Date:May 20, 2003

HFD-170 Trade and generic names/dosage form: Duragesic® (Fentanyl Transdermal System)

Applicant: Alza Corporation Therapeutic Class: N/A for supplements

Indication(s) previously approved:
The management of chronic pain in patients who require continuous opioid analgesia for pain that cannot be managed by lesser means such as acetaminophen-opioid combinations, non-steroidal analgesics, or PRN dosing with short-acting opioids.

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 1

Indication #1: same as currently approved indication (This supplement did not add to or change the currently approved indication, it simply added information on the use of the product in pediatric patients 2 years of age and older.)

Is there a full waiver for this indication (check one)?

- ☐ Yes: Please proceed to Section A.
- ■ No: Please check all that apply: ____Partial Waiver X Deferred X Completed
  NOTE: More than one may apply
  Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ☐ Products in this class for this indication have been studied/labeled for pediatric population
- ☐ Disease/condition does not exist in children
- ☐ Too few children with disease to study
- ☐ There are safety concerns
- ☐ Other:_____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min_____	kg_____	mo._____	yr. ____	Tanner Stage_____	
Max_____	kg_____	mo._____	yr. ____	Tanner Stage_____	

Reason(s) for partial waiver:

- ☐ Products in this class for this indication have been studied/labeled for pediatric population
- ☐ Disease/condition does not exist in children
- ☐ Too few children with disease to study
- ☐ There are safety concerns

- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:**_____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____	**kg**_____	**mo.**_____	**yr.** 0	**Tanner Stage**_____
Max_____	**kg**_____	**mo.**_____	**yr.** 2	**Tanner Stage**_____

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ■ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ■ **Formulation needed**

Other:_____

Date studies are due (mm/dd/yy): May 31, 2005

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____	**kg**_____	**mo.**_____	**yr.** 2	**Tanner Stage**_____
Max_____	**kg**_____	**mo.**_____	**yr.**17	**Tanner Stage**_____

Comments: This supplement provided information for use of the product in 2-17 year olds.

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}
Kimberly Compton,
Regulatory Project Manager

cc: NDA
HFD-950/ Terrie Crescenzi
HFD-960/ Grace Carmouze
(revised 9-24-02)

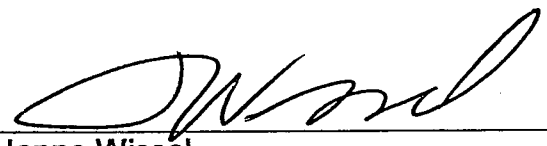
SECTION 19: FINANCIAL INFORMATION (CERTIFICATION AND DISCLOSURE)

In accordance with 21 CFR Part 54, financial information was obtained from key personnel who participated in studies FEN-USA-87 and FEN-INT-24 to permit appropriate Certification (attached Form FDA 3454) and Disclosure (attached Forms FDA 3455).

Financial information was not obtained for studies FEN-GBR-14 and FEN-FRA-4 as these studies were conducted prior to implementation of the regulations outlined in 21 CFR Part 54.

SECTION 16: DEBARMENT CERTIFICATION

ALZA Corporation hereby certifies that it did not and will not use in any capacity the services of any person(s) or firm debarred under section 306 of the Federal Food, Drug, and Cosmetic Act, as amended, in connection with this application.



20 Nov 02

Janne Wissel
Senior Vice President
Operations

Date

SECTION 20: OTHER
ENVIRONMENTAL ASSESSMENT-
CLAIM FOR CATEGORICAL EXCLUSION

ALZA Corporation herewith submits a claim for categorical exclusion from preparation of an environmental assessment under 21 CFR 25.31(b).

The requested action is for approval of a supplemental NDA for Duragesic® (fentanyl transdermal system) [NDA no. 19-813] to meet the terms of the Pediatric Written Request. Action on the sNDA may increase the use of the active moiety (fentanyl), but the estimated concentration of the substance at the point of entry into the aquatic environment is calculated to be below one part per billion (ppb).

To the best of the applicant's knowledge, no extraordinary circumstances exist.