CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

19-813 / S - 039

Trade Name: Duragesic

Generic Name: Fentanyl Transdermal System

Sponsor: Alza Corporation

Approval Date: February 4, 2005

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APPLICATION NUMBER:

19-813 / S - 039

CONTENTS

Reviews / Information Included in this NDA Review.

Approval Letter	X
Approvable Letter	
Labeling	X
Summary Review	
Officer/Employee List	
Office Director Memo	
Cross Discipline Team Leader Review	
Medical Review(s)	X
Chemistry Review(s)	
Environmental Assessment	
Pharmacology Review(s)	
Statistical Review(s)	
Microbiology Review(s)	
Clinical Pharmacology/Biopharmaceutics Review(s)	X
Risk Assessment and Risk Mitigation Review(s)	
Proprietary Name Review(s)	
Administrative/Correspondence Document(s)	X

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APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 19-813/S-039

Alza Corporation
1900 Charleston Road
Mountain View, CA 94043

Attention: Susan P. Rinne, M.S.
Vice President, Regulatory Affairs

Dear Ms. Rinne:

Please refer to your supplemental new drug application dated April 5, 2004, received April 6, 2004, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Duragesic® (Fentanyl Transdermal System).

We acknowledge receipt of your submissions dated July 9 and 29, and November 24, 2004, and January 24, February 1 and 3, 2005.

We also acknowledge receipt of your September 10, 2004, submission for Supplement S-031 in response to our June 10, 2003, Approvable Letter for that supplement. The labeling for S-031 is now superceded by the labeling approved with this supplement.

This supplemental new drug application provides for the use of Duragesic® (Fentanyl Transdermal System) 12 mcg/h patch for the management of persistent, moderate to severe chronic pain that: requires continuous, around-the-clock opioid administration for an extended period of time, and cannot be managed by other means such as non-steroidal analgesics, opioid combination products, or immediate-release opioids.

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 and submitted labeling (immediate container and carton labels submitted November 24, 2004).

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format – NDA* and *Providing Regulatory Submissions in Electronic Format-Content of Labeling*. Alternatively, except for the content of labeling, which must be submitted electronically in PDF format, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, designate this submission "**FPL for approved supplement NDA 19-813/S-039.**" Approval of this submission by FDA is not required before the labeling is used.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have fulfilled the pediatric study requirement for this application for patients 2 years of age and over. We are waiving the requirement for patients from birth to 2 years of age.

We remind you of your agreement to lower the limits [redacted]

We also remind you of your agreement during our February 4, 2005 teleconference to continue discussions with the Agency regarding establishment of a risk management program for this product.

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, HFD-410
FDA
5600 Fishers Lane
Rockville, MD 20857

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.
Director
Division of Anesthetic, Critical Care, and
Addiction Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure

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
2/4/05 07:50:23 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-813 / S - 039

LABELING

DURAGESIC®
(FENTANYL TRANSDERMAL SYSTEM) CII

Full Prescribing Information

FOR USE IN OPIOID-TOLERANT PATIENTS ONLY

DURAGESIC® contains a high concentration of a potent Schedule II opioid agonist, fentanyl. Schedule II opioid substances which include fentanyl, hydromorphone, methadone, morphine, oxycodone, and oxymorphone have the highest potential for abuse and associated risk of fatal overdose due to respiratory depression. Fentanyl can be abused and is subject to criminal diversion. The high content of fentanyl in the patches (DURAGESIC®) may be a particular target for abuse and diversion.

DURAGESIC® is indicated for management of persistent, moderate to severe chronic pain that:

- **requires continuous, around-the-clock opioid administration for an extended period of time, and**
- **cannot be managed by other means such as non-steroidal analgesics, opioid combination products, or immediate-release opioids**

DURAGESIC® should ONLY be used in patients who are already receiving opioid therapy, who have demonstrated opioid tolerance, and who require a total daily dose at least equivalent to DURAGESIC® 25 mcg/h. Patients who are considered opioid-tolerant are those who have been taking, for a week or longer, at least 60 mg of morphine daily, or at least 30 mg of oral oxycodone daily, or at least 8 mg of oral hydromorphone daily or an equianalgesic dose of another opioid.

Because serious or life-threatening hypoventilation could occur, DURAGESIC® (fentanyl transdermal system) is contraindicated:

- **in patients who are not opioid-tolerant**
- **in the management of acute pain or in patients who require opioid analgesia for a short period of time**
- **in the management of post-operative pain, including use after out-patient or day surgeries (e.g., tonsillectomies)**
- **in the management of mild pain**
- **in the management of intermittent pain [e.g., use on an as needed basis (prn)]**

(See CONTRAINDICATIONS for further information.)
Since the peak fentanyl levels occur between 24 and 72 hours of treatment, prescribers should be aware that serious or life threatening hypoventilation may occur, even in opioid-tolerant patients, during the initial application period.

The concomitant use of DURAGESIC® with potent cytochrome P450 3A4 inhibitors (ritonavir, ketoconazole, itraconazole, troleandomycin, clarithromycin, nelfinavir, and nefazodone) may result in an increase in fentanyl plasma concentrations, which could increase or prolong adverse drug effects and may cause potentially fatal respiratory depression. Patients receiving DURAGESIC® and potent CYP3A4 inhibitors should be carefully monitored for an extended period of time and dosage adjustments should be made if warranted. (See CLINICAL PHARMACOLOGY – Drug Interactions, WARNINGS, PRECAUTIONS and DOSAGE AND ADMINISTRATION for further information.)

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 2 years of age or older (see PRECAUTIONS - Pediatric Use).

DURAGESIC® is ONLY for use in patients who are already tolerant to opioid therapy of comparable potency. Use in non-opioid tolerant patients may lead to fatal respiratory depression. Overestimating the DURAGESIC® dose when converting patients from another opioid medication can result in fatal overdose with the first dose. Due to the mean elimination half-life of 17 hours of DURAGESIC®, patients who are thought to have had a serious adverse event, including overdose, will require monitoring and treatment for at least 24 hours.

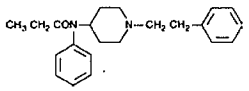
DURAGESIC® can be abused in a manner similar to other opioid agonists, legal or illicit. This risk should be considered when administering, prescribing, or dispensing DURAGESIC® in situations where the healthcare professional is concerned about increased risk of misuse, abuse or diversion.

Persons at increased risk for opioid abuse include those with a personal or family history of substance abuse (including drug or alcohol abuse or addiction) or mental illness (e.g., major depression). Patients should be assessed for their clinical risks for opioid abuse or addiction prior to being prescribed opioids. All patients receiving opioids should be routinely monitored for signs of misuse, abuse and addiction. Patients at increased risk of opioid abuse may still be appropriately treated with modified-release opioid formulations; however, these patients will require intensive monitoring for signs of misuse, abuse, or addiction.

DURAGESIC® patches are intended for transdermal use (on intact skin) only. Using damaged or cut DURAGESIC® patches can lead to the rapid release of the contents of the DURAGESIC® patch and absorption of a potentially fatal dose of fentanyl.

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-piperidinyl) 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 mcg/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.

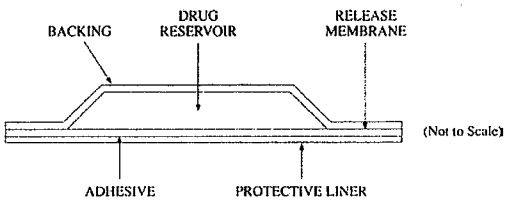
Dose* (mcg/h)	Size (cm2)	Fentanyl Content (mg)
12**	5	1.25
25	10	2.5
50	20	5
75	30	7.5
100	40	10

* Nominal delivery rate per hour

** Nominal delivery rate is 12.5 mcg/hr

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, which can lead to the rapid release and absorption of a potentially fatal dose of fentanyl.

CLINICAL PHARMACOLOGY

Pharmacology

Fentanyl is an opioid analgesic. Fentanyl interacts predominately with the opioid mu-receptor. These mu-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.

In addition to analgesia, alterations in mood, euphoria, 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 clinical studies indicate that clinically significant histamine release rarely occurs with fentanyl administration. Clinical assays show no clinically significant histamine release in dosages up to 50 mcg/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 (12.5, 25, 50, 75, and 100 mcg 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 mcg/h (n=10)

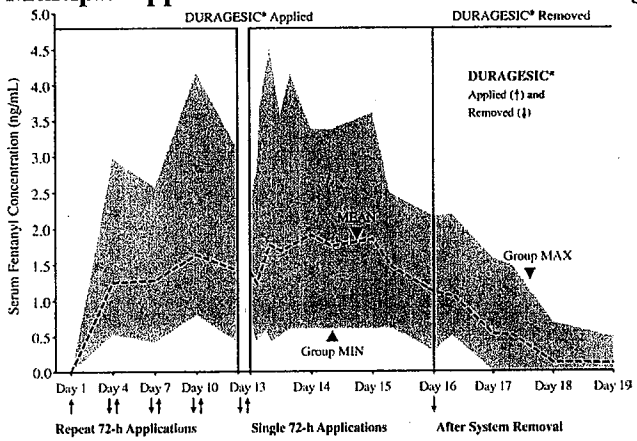


TABLE A
FENTANYL PHARMACOKINETIC PARAMETERS
FOLLOWING FIRST 72-HOUR APPLICATION OF DURAGESIC®

	Mean (SD) Time to Maximal Concentration Tmax (h)	Mean (SD) Maximal Concentration Cmax (ng/mL)
DURAGESIC® 12 mcg/h	27.5 (9.6)	0.3 (0.2)
DURAGESIC® 25 mcg/h	38.1 (18.0)	0.6 (0.3)
DURAGESIC® 50 mcg/h	34.8 (15.4)	1.4 (0.5)
DURAGESIC® 75 mcg/h	33.5 (14.5)	1.7 (0.7)
DURAGESIC® 100 mcg/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 VSS (L/kg) Range	Half-Life t1/2 (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 to 5 year old, non-opioid-tolerant pediatric patients, the fentanyl plasma concentrations were approximately twice as high as that of adult patients. In older pediatric patients, the pharmacokinetic parameters were similar to that of adults. However, these findings have been taken into consideration in determining the dosing recommendations for opioid-tolerant pediatric patients (2 years of age and older). For pediatric dosing information, refer to DOSAGE AND ADMINISTRATION section.

The kinetics of fentanyl in geriatric patients have 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.

Drug interactions
The interaction between ritonavir and fentanyl was investigated in eleven healthy volunteers in a randomized crossover study. Subjects received oral ritonavir or placebo for 3 days. The ritonavir dose was 200 mg tid on Day 1 and 300 mg tid on Day 2 followed by one morning dose of 300 mg on Day 3. On Day 2, fentanyl was given as a single IV dose at 5 mcg/kg two hours after the afternoon dose of oral ritonavir or placebo. Naloxone was administered to counteract the side effects of fentanyl. The results suggested that ritonavir might decrease the clearance of fentanyl by 67%, resulting in a 174% (range 52%-420%) increase in fentanyl $AUC_{0-\infty}$. Coadministration of ritonavir in patients receiving DURAGESIC® has not been studied; however, an increase in fentanyl AUC is expected. (See BOX WARNING, WARNINGS, DOSAGE AND ADMINISTRATION and PRECAUTIONS.)

PHARMACODYNAMICS

Ventilatory Effects
Because of the risk for serious or life-threatening hypoventilation, DURAGESIC® is CONTRAINDICATED in the treatment of post-operative and acute pain and in patients who are not opioid-tolerant. In clinical trials of 357 patients with acute pain treated with DURAGESIC®, 13 patients experienced hypoventilation. Hypoventilation was manifested by respiratory rates of less than 8 breaths/minute or a pCO_2 greater than 55 mm Hg. 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 that describe opioid-naive post-operative patients who have experienced clinically significant hypoventilation and death with DURAGESIC®.

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. Hypoventilation can occur throughout the therapeutic range of fentanyl serum concentrations, 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 DURAGESIC® is contraindicated in patients who are not tolerant to opioid therapy. The use of DURAGESIC® should be monitored by clinical evaluation, especially within the initial 24-72 hours when serum concentrations from the initial patch will peak, and following increases in dosage. DURAGESIC® should be administered to children only if they are opioid-tolerant and 2 years of age or older.

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
Central nervous system effects increase with increasing serum fentanyl concentrations.

INDICATIONS AND USAGE

DURAGESIC® is indicated for management of persistent, moderate to severe chronic pain that:

- requires continuous, around-the-clock opioid administration for an extended period of time, and
- cannot be managed by other means such as non-steroidal analgesics, opioid combination products, or immediate-release opioids

DURAGESIC® should ONLY be used in patients who are already receiving opioid therapy, who have demonstrated opioid tolerance, and who require a total daily dose at least equivalent to DURAGESIC® 25 mcg/h (see DOSAGE AND ADMINISTRATION). Patients who are considered opioid-tolerant are those who have been taking, for a week or longer, at least 60 mg of morphine daily, or at least 30 mg of oral oxycodone daily, or at least 8 mg of oral hydromorphone daily, or an equianalgesic dose of another opioid.

Because serious or life-threatening hypoventilation could result, DURAGESIC® is contraindicated for use on an as needed basis (i.e., prn), for the management of post-operative or acute pain, or in patients who are not opioid-tolerant or who require opioid analgesia for a short period of time. (see BOX WARNING and CONTRAINDICATIONS).

An evaluation of the appropriateness and adequacy of treating with immediate-release opioids is advisable prior to initiating therapy with any modified-release opioid. Prescribers should individualize treatment in every case, initiating therapy at the appropriate point along a progression from non-opioid analgesics, such as non-steroidal anti-inflammatory drugs and acetaminophen, to opioids, in a plan of pain management such as outlined by the World Health Organization, the Agency for Health Research and Quality, the Federation of State Medical Boards Model Policy, or the American Pain Society.

Patients should be assessed for their clinical risks for opioid abuse or addiction prior to being prescribed opioids. Patients receiving opioids should be routinely monitored for signs of misuse, abuse, and addiction. Persons at increased risk for opioid abuse include those with a personal or family history of substance abuse (including drug or alcohol abuse or addiction) or mental illness (e.g., major depression). Patients at increased risk may still be appropriately treated with modified-release opioid formulations; however these patients will require intensive monitoring for signs of misuse, abuse, or addiction.

CONTRAINDICATIONS

Because serious or life-threatening hypoventilation could occur, DURAGESIC® (fentanyl transdermal system) is contraindicated:

- **in patients who are not opioid-tolerant**
- **in the management of acute pain or in patients who require opioid analgesia for a short period of time**
- **in the management of post-operative pain, including use after out-patient or day surgeries, (e.g., tonsillectomies)**
- **in the management of mild pain**
- **in the management of intermittent pain (e.g., use on an as needed basis [prn])**
- **in situations of significant respiratory depression, especially in unmonitored settings where there is a lack of resuscitative equipment**
- **in patients who have acute or severe bronchial asthma**

DURAGESIC® (fentanyl transdermal system) is contraindicated in patients who have or are suspected of having paralytic ileus.

DURAGESIC® (fentanyl transdermal system) is contraindicated in patients with known hypersensitivity to fentanyl or any components of this product.

WARNINGS

DURAGESIC® patches are intended for transdermal use (on intact skin) only. Using damaged or cut DURAGESIC® patches can lead to the rapid release of the contents of the DURAGESIC® patch and absorption of a potentially fatal dose of fentanyl.

The safety of DURAGESIC® (fentanyl transdermal system) has not been established in children under 2 years of age. DURAGESIC® should be administered to children only if they are opioid-tolerant and 2 years of age or older (see PRECAUTIONS - Pediatric Use).

DURAGESIC® is ONLY for use in patients who are already tolerant to opioid therapy of comparable potency. Use in non-opioid tolerant patients may lead to fatal respiratory depression. Overestimating the DURAGESIC® dose when converting patients from another opioid medication can result in fatal overdose with the first dose. The mean elimination half-life of DURAGESIC® is 17 hours. Therefore, patients who have experienced serious adverse events, including overdose, will require monitoring for at least 24 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.

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 released from the system resulting in possible overdose and death (see PRECAUTIONS - Patients with Fever/External Heat).

Death and other serious medical problems have occurred when people were accidentally exposed to DURAGESIC®. Examples of accidental exposure include transfer of a DURAGESIC® patch from an adult's body to a child while hugging, accidental sitting on a patch and possible accidental exposure of a caregiver's skin to the medication in the patch while the caregiver was applying or removing the patch.

Placing DURAGESIC® in the mouth, chewing it, swallowing it, or using it in ways other than indicated may cause choking or overdose that could result in death.

Misuse, Abuse and Diversion of Opioids
Fentanyl is an opioid agonist of the morphine-type. Such drugs are sought by drug abusers and people with addiction disorders and are subject to criminal diversion.

Fentanyl can be abused in a manner similar to other opioids, legal or illicit. This should be considered when prescribing or dispensing DURAGESIC® in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse or diversion.

DURAGESIC® has been reported as being abused by other methods and routes of administration. These practices will result in uncontrolled delivery of the opioid and pose a significant risk to the abuser that could result in overdose and death (see WARNINGS and DRUG ABUSE AND ADDICTION).

Concerns about abuse, addiction and diversion should not prevent the proper management of pain. However, all patients treated with opioids require careful monitoring for signs of abuse and addiction, since use of opioid analgesic products carries the risk of addiction even under appropriate medical use.

Healthcare professionals should contact their state professional licensing board or state controlled substances authority for information on how to prevent and detect abuse or diversion of this product.

Hypoventilation (Respiratory Depression)
Serious or life-threatening hypoventilation may occur at any time during the use of DURAGESIC® especially during the initial 24-72 hours following initiation of therapy and following increases in dose.

Because significant amounts of fentanyl are absorbed from the skin for 17 hours or more after the patch 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.

Respiratory depression is the chief hazard of opioid agonists, including fentanyl the active ingredient in DURAGESIC®. Respiratory depression is more likely to occur in elderly or debilitated patients, usually following large initial doses in non- tolerant patients, or when opioids are given in conjunction with other drugs that depress respiration.

Respiratory depression from opioids is manifested by a reduced urge to breathe and a decreased rate of respiration, often associated with the "sighing" pattern of breathing (deep breaths separated by abnormally long pauses). Carbon dioxide retention from opioid-induced respiratory depression can exacerbate the sedating effects of opioids. This makes overdoses involving drugs with sedative properties and opioids especially dangerous.

DURAGESIC® should be used with extreme caution in patients with significant chronic obstructive pulmonary disease or cor pulmonale, and in patients having a substantially decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression. In such patients, even usual therapeutic doses of DURAGESIC® may decrease respiratory drive to the point of apnea. In these patients, alternative non-opioid analgesics should be considered, and opioids should be employed only under careful medical supervision at the lowest effective dose.

Chronic Pulmonary Disease
Because potent opioids can cause serious or life-threatening hypoventilation, DURAGESIC® 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.

Interactions with other CNS Depressants
The concomitant use of DURAGESIC® (fentanyl transdermal system) with other central nervous system depressants, including but not limited to other opioids, sedatives, hypnotics, tranquilizers (e.g., benzodiazepines), general anesthetics, phenothiazines, skeletal muscle relaxants, and alcohol, may cause respiratory depression, hypotension, and profound sedation or potentially result in coma. When such combined therapy is contemplated, the dose of one or both agents should be significantly reduced.

Interactions with Alcohol and Drugs of Abuse
Fentanyl may be expected to have additive CNS depressant effects when used in conjunction with alcohol, other opioids, or illicit drugs that cause central nervous system depression.

Interactions with CYP3A4 Inhibitors
The concomitant use of DURAGESIC® with potent cytochrome P450 3A4 inhibitors (ritonavir, ketoconazole, itraconazole, troleandomycin, clarithromycin, nelfinavir, and nefazodone) may result in an increase in fentanyl plasma concentrations, which could increase or prolong adverse drug effects and may cause potentially fatal respiratory depression. Patients receiving DURAGESIC® and potent CYP3A4 inhibitors should be carefully monitored for an extended period of time and dosage adjustments should be made if warranted. (See BOX WARNING, CLINICAL PHARMACOLOGY – Drug Interactions, PRECAUTIONS and DOSAGE AND ADMINISTRATION for further information.)

PRECAUTIONS

General
DURAGESIC® (fentanyl transdermal system) should not be used to initiate opioid therapy in patients who are not opioid-tolerant. Children converting to DURAGESIC® should be opioid-tolerant and 2 years of age or older (see BOX WARNING.)

Patients, family members and caregivers should be instructed to keep patches (new and used) out of the reach of children and others for whom DURAGESIC® was not prescribed. A considerable amount of active fentanyl remains in DURAGESIC® even after use as directed. Accidental or deliberate application or ingestion by a child or adolescent will cause respiratory depression that could result in death.

Cardiac Disease
Fentanyl may produce bradycardia. Fentanyl should be administered with caution to patients with bradyarrhythmias.

Hepatic or Renal Disease
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 released 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.

Use in Pancreatic/Biliary Tract Disease
DURAGESIC® may cause spasm of the sphincter of Oddi and should be used with caution in patients with biliary tract disease, including acute pancreatitis. Opioids like DURAGESIC® may cause increases in the serum amylase concentration.

Tolerance
Tolerance is a state of adaptation in which exposure to a drug induces changes that result in a diminution of one or more of the drug's effects over time. Tolerance may occur to

both the desired and undesired effects of drugs, and may develop at different rates for different effects.

Physical Dependence
Physical dependence is a state of adaptation that is manifested by an opioid specific withdrawal syndrome that can be produced by abrupt cessation, rapid dose reduction, decreasing blood level of the drug, and/or administration of an antagonist. The opioid abstinence or withdrawal syndrome is characterized by some or all of the following: restlessness, lacrimation, rhinorrhea, yawning, perspiration, chills, piloerection, myalgia, mydriasis, irritability, anxiety, backache, joint pain, weakness, abdominal cramps, insomnia, nausea, anorexia, vomiting, diarrhea, or increased blood pressure, respiratory rate, or heart rate. In general, opioids should not be abruptly discontinued (see **DOSAGE AND ADMINISTRATION**: **Cessation of Therapy**).

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.

Information for Patients
A patient information sheet is included in the package of DURAGESIC® patches dispensed to the patient.

Patients receiving DURAGESIC® patches should be given the following instructions by the physician:

1. Patients should be advised that DURAGESIC® patches contain fentanyl, an opioid pain medicine similar to morphine, hydromorphone, methadone, oxycodone, and oxymorphone.
2. Patients should be advised that each DURAGESIC® patch may be worn continuously for 72 hours, and that each patch should be applied to a different skin site after removal of the previous transdermal patch.
3. Patients should be advised that DURAGESIC® patches should be applied to intact, non-irritated, and non-irradiated skin on a flat surface such as the chest, back, flank, or upper arm. Additionally, patients should be advised of the following:
    - In young children or persons with cognitive impairment, the patch should be put on the upper back to lower the chances that the patch will be removed and placed in the mouth.
    - Hair at the application site should be clipped (not shaved) prior to patch application.
    - If the site of DURAGESIC® application must be cleansed prior to application of the patch, 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 patch application.

4. Patients should be advised that DURAGESIC® should be applied immediately upon removal from the sealed package and after removal of the protective liner. Additionally the patient should be advised of the following:
    - The DURAGESIC® patch should not be used if the seal is broken, or if it is altered, cut, or damaged in any way prior to application. This could lead to the rapid release of the contents of the DURAGESIC® patch and absorption of a potentially fatal dose of fentanyl. The transdermal patch 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.
    - The patch should not be folded so that only part of the patch is exposed.
5. Patients should be advised that while wearing the patch, they should avoid exposing the DURAGESIC® application site to direct external heat sources, such as:
    - heating pads,
    - electric blankets,
    - heat lamps,
    - saunas,
    - hot tubs, and
    - heated water beds, etc.,
6. Patients should be advised that there is a potential for temperature-dependent increase in fentanyl release from the patch that could result in an overdose of fentanyl; therefore, if patients develop a high fever while wearing the patch they should contact their physician.
7. Patients should be advised to fold (so that the adhesive side adheres to itself) and immediately flush down the toilet used DURAGESIC® patches after removal from the skin.
8. Patients should be instructed that, if the gel from the drug reservoir accidentally contacts the skin, the area should be washed clean with clear water and not soap, alcohol, or other chemicals, because these products may increase the ability of fentanyl to go through the skin.
9. Patients should be advised that the dose of DURAGESIC® should NEVER be adjusted without the prescribing health care professional's instruction.
10. Patients should be advised that DURAGESIC® may impair mental and/or physical ability required for the performance of potentially hazardous tasks (e.g., driving, operating machinery).
11. Patients should be advised to refrain from any potentially dangerous activity when starting on DURAGESIC® or when their dose is being adjusted, until it is established that they have not been adversely affected.

12. Patients should be advised that DURAGESIC® should not be combined with alcohol or other CNS depressants (e.g. sleep medications, tranquilizers) because dangerous additive effects may occur, resulting in serious injury or death.
13. Patients should be advised to consult their physician or pharmacist if other medications are being or will be used with DURAGESIC®.
14. Patients should be advised of the potential for severe constipation.
15. Patients should be advised that if they have been receiving treatment with DURAGESIC® and cessation of therapy is indicated, it may be appropriate to taper the DURAGESIC® dose, rather than abruptly discontinue it, due to the risk of precipitating withdrawal symptoms.
16. Patients should be advised that DURAGESIC® contains fentanyl, a drug with high potential for abuse.
17. Patients, family members and caregivers should be advised to protect DURAGESIC® from theft or misuse in the work or home environment.
18. Patients should be advised that DURAGESIC® should never be given to anyone other than the individual for whom it was prescribed because of the risk of death or other serious medical problems to that person for whom it was not intended.
19. Patients should be instructed to keep DURAGESIC® in a secure place out of the reach of children due to the high risk of **fatal respiratory depression**.
20. When DURAGESIC® is no longer needed, the unused patches should be removed from their pouches, folded so that the adhesive side of the patch adheres to itself, and flushed down the toilet.
21. Women of childbearing potential who become, or are planning to become pregnant, should be advised to consult a physician prior to initiating or continuing therapy with DURAGESIC®.
22. Patients should be informed that accidental exposure or misuse may lead to death or other serious medical problems.
23. Patients should be informed that, if the patch dislodges and accidentally sticks to skin of another person, they should immediately take the patch off, wash the exposed area with water and seek medical attention for the accidentally exposed individual.

Drug Interactions

Agents Affecting Cytochrome P450 3A4 Isoenzyme System

Fentanyl is metabolized mainly via the human cytochrome P450 3A4 isoenzyme system (CYP3A4), therefore potential interactions may occur when DURAGESIC® is given concurrently with agents that affect CYP3A4 activity. Coadminstration with agents that induce 3A4 activity may reduce the efficacy of DURAGESIC®. The concomitant use of transdermal fentanyl with ritonavir or other potent 3A4 inhibitors such as ketoconazole, itraconazole, troleandomycin, clarithromycin, nelfinavir, and nefazadone may result in an increase in fentanyl plasma concentrations (see BOX WARNING, CLINICAL PHARMACOLOGY – Drug Interactions , WARNINGS, and DOSAGE AND ADMINISTRATION). The concomitant use of other CYP3A4 inhibitors such as

diltiazem and erythromycin with transdermal fentanyl may also result in an increase in fentanyl plasma concentrations, which could increase or prolong adverse drug effects and may cause serious respiratory depression. In this situation, special patient care and observation are appropriate.

Central Nervous System Depressants
The concomitant use of DURAGESIC® (fentanyl transdermal system) with other central nervous system depressants, including but not limited to other opioids, sedatives, hypnotics, tranquilizers (e.g., benzodiazepines), general anesthetics, phenothiazines, skeletal muscle relaxants, and alcohol, may cause respiratory depression, hypotension, and profound sedation, or potentially result in coma or death. When such combined therapy is contemplated, the dose of one or both agents should be significantly reduced.

MAO Inhibitors
DURAGESIC® is not recommended for use in patients who have received MAOI within 14 days because severe and unpredictable potentiation by MAO inhibitors has been reported with opioid analgesics.

Carcinogenesis, Mutagenesis, and Impairment of Fertility
Studies in animals to evaluate the carcinogenic potential of fentanyl HCl have not been conducted. There was no evidence of mutagenicity in the Ames Salmonella mutagenicity assay, the primary rat hepatocyte unscheduled DNA synthesis assay, the BALB/c 3T3 transformation test, and the human lymphocyte and CHO chromosomal aberration in-vitro assays.

The potential effects of fentanyl on male and female fertility were examined in the rat model via two separate experiments. In the male fertility study, male rats were treated with fentanyl (0, 0.025, 0.1 or 0.4 mg/kg/day) via continuous intravenous infusion for 28 days prior to mating; female rats were not treated. In the female fertility study, female rats were treated with fentanyl (0, 0.025, 0.1 or 0.4 mg/kg/day) via continuous intravenous infusion for 14 days prior to mating until day 16 of pregnancy; male rats were not treated. Analysis of fertility parameters in both studies indicated that an intravenous dose of fentanyl up to 0.4 mg/kg/day to either the male or the female alone produced no effects on fertility (this dose is approximately 1.6 times the daily human dose administered by a 100 mcg/hr patch on a mg/m^2 basis). In a separate study, a single daily bolus dose of fentanyl was shown to impair fertility in rats when given in intravenous doses of 0.3 times the human dose for a period of 12 days.

Pregnancy – Pregnancy Category C
No epidemiological studies of congenital anomalies in infants born to women treated with fentanyl during pregnancy have been reported.

The potential effects of fentanyl on embryo-fetal development were studied in the rat, mouse, and rabbit models. Published literature reports that administration of fentanyl (0,

10, 100, or 500 μg/kg/day) to pregnant female Sprague-Dawley rats from day 7 to 21 via implanted microosmotic minipumps did not produce any evidence of teratogenicity (the high dose is approximately 2 times the daily human dose administered by a 100 mcg/hr patch on a mg/m^2 basis). In contrast, the intravenous administration of fentanyl (0, 0.01, or 0.03 mg/kg) to bred female rats from gestation day 6 to 18 suggested evidence of embryotoxicity and a slight increase in mean delivery time in the 0.03 mg/kg/day group. There was no clear evidence of teratogenicity noted.

Pregnant female New Zealand White rabbits were treated with fentanyl (0, 0.025, 0.1, 0.4 mg/kg) via intravenous infusion from day 6 to day 18 of pregnancy. Fentanyl produced a slight decrease in the body weight of the live fetuses at the high dose, which may be attributed to maternal toxicity. Under the conditions of the assay, there was no evidence for fentanyl induced adverse effects on embryo-fetal development at doses up to 0.4 mg/kg (approximately 3 times the daily human dose administered by a 100 mcg/hr patch on a mg/m^2 basis).

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.

Nonteratogenic Effects
Chronic maternal treatment with fentanyl during pregnancy has been associated with transient respiratory depression, behavioral changes, or seizures characteristic of neonatal abstinence syndrome in newborn infants. Symptoms of neonatal respiratory or neurological depression were no more frequent than expected in most studies of infants born to women treated acutely during labor with intravenous or epidural fentanyl. Transient neonatal muscular rigidity has been observed in infants whose mothers were treated with intravenous fentanyl.

The potential effects of fentanyl on prenatal and postnatal development were examined in the rat model. Female Wistar rats were treated with 0, 0.025, 0.1, or 0.4 mg/kg/day fentanyl via intravenous infusion from day 6 of pregnancy through 3 weeks of lactation. Fentanyl treatment (0.4 mg/kg/day) significantly decreased body weight in male and female pups and also decreased survival in pups at day 4. Both the mid-dose and high-dose of fentanyl animals demonstrated alterations in some physical landmarks of development (delayed incisor eruption and eye opening) and transient behavioral development (decreased locomotor activity at day 28 which recovered by day 50). The mid-dose and the high-dose are 0.4 and 1.6 times the daily human dose administered by a 100 mcg/hr patch on a mg/m^2 basis.

Labor and Delivery
Fentanyl readily passes across the placenta to the fetus; therefore, 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
The safety of DURAGESIC® was evaluated in three open-label trials in 291 pediatric patients with chronic pain, 2 years of age through 18 years of age. Starting doses of 25 mcg/h and higher were used by 181 patients who had been on prior daily opioid doses of at least 45 mg/day of oral morphine or an equianalgesic dose of another opioid. Initiation of DURAGESIC® therapy in pediatric patients taking less than 60 mg/day of oral morphine or an equianalgesic dose of another opioid has not been evaluated in controlled clinical trials. Approximately 90% of the total daily opioid requirement (DURAGESIC® plus rescue medication) was provided by DURAGESIC®.

DURAGESIC® was not studied in children under 2 years of age.

DURAGESIC® should be administered to children only if they are opioid-tolerant and 2 years of age 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 (N=4) indicates that the clearance of fentanyl may be greatly decreased in the population above the age of 60. The relevance of these findings to DURAGESIC® (fentanyl transdermal system) 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 mcg/h unless they are already tolerating an around-the-clock opioid at a dose and potency comparable to DURAGESIC®-25 (see DOSAGE AND ADMINISTRATION).

Respiratory depression is the chief hazard in elderly or debilitated patients, usually following large initial doses in non-tolerant patients, or when opioids are given in conjunction with other agents that depress respiration.

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
Although DURAGESIC® use in post-operative or acute pain and in patients who are not opioid-tolerant is CONTRAINDICATED, the safety of DURAGESIC® was originally evaluated in 357 post-operative adult patients for 1 to 3 days and 153 cancer patients for a total of 510 patients. 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%) post-operative 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 post-operative patients.

In the pediatric population, the safety of DURAGESIC® has been evaluated in 291 patients with chronic pain 2-18 years of age. 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=380) and Pediatric (N=291) Clinical Trial Experience

Body System	Adults	Pediatrics
Body as a Whole	Abdominal pain*, headache*, fatigue*, back pain, fever, influenza-like symptoms*, accidental injury, rigors	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**, insomnia, 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*, apnea*, hemoptysis, pharyngitis*, hiccups, bronchitis, rhinitis, sinusitis, upper respiratory tract infection*	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* Micturition disorder	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 post-operative and cancer patients studied:
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 have been reported in association with the use of DURAGESIC® and not reported in the pre-marketing adverse reactions section above:
Body as a Whole: edema
Cardiovascular: tachycardia
Metabolic and Nutritional: weight loss
Special Senses: blurred vision
Urogenital: decreased libido, anorgasmia, ejaculatory difficulty

DRUG ABUSE AND ADDICTION
DURAGESIC® contains a high concentration of fentanyl, a potent Schedule II opioid agonist. Schedule II opioid substances, which include hydromorphone, methadone, morphine, oxycodone, and oxymorphone, have the highest potential for abuse and risk of fatal overdose due to respiratory depression. Fentanyl, like morphine and other opioids used in analgesia, can be abused and is subject to criminal diversion.

The high content of fentanyl in the patches (DURAGESIC®) may be a particular target for abuse and diversion.

Addiction is a primary, chronic, neurobiologic disease, with genetic, psychosocial, and environmental factors influencing its development and manifestations. It is characterized by behaviors that include one or more of the following: impaired control over drug use, compulsive use, continued use despite harm, and craving. Drug addiction is a treatable disease, utilizing a multidisciplinary approach, but relapse is common.

"Drug seeking" behavior is very common in addicts and drug abusers. Drug-seeking tactics include emergency calls or visits near the end of office hours, refusal to undergo appropriate examination, testing or referral, repeated "loss" of prescriptions, tampering with prescriptions and reluctance to provide prior medical records or contact information for other treating physician(s). "Doctor shopping" to obtain additional prescriptions is common among drug abusers and people suffering from untreated addiction.

Abuse and addiction are separate and distinct from physical dependence and tolerance. Physicians should be aware that addiction may be accompanied by concurrent tolerance

and symptoms of physical dependence. In addition, abuse of opioids can occur in the absence of true addiction and is characterized by misuse for non-medical purposes, often in combination with other psychoactive substances. Since DURAGESIC® may be diverted for non-medical use, careful record keeping of prescribing information, including quantity, frequency, and renewal requests is strongly advised.
Proper assessment of the patient, proper prescribing practices, periodic re-evaluation of therapy, and proper dispensing and storage are appropriate measures that help to limit abuse of opioid drugs.

DURAGESIC® patches are intended for transdermal use (to be applied on the skin) only. Using cut or damaged DURAGESIC® patches or its contents can lead to the rapid release and absorption of a potentially fatal dose of fentanyl.

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.

Always 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

Special Precautions
DURAGESIC® contains a high concentration of a potent Schedule II opioid agonist, fentanyl. Schedule II opioid substances which include fentanyl, hydromorphone, methadone, morphine, oxycodone, and oxymorphone have the highest potential for abuse and associated risk of fatal overdose due to respiratory depression. Fentanyl

can be abused and is subject to criminal diversion. The high content of fentanyl in the patches (DURAGESIC®) may be a particular target for abuse and diversion.

DURAGESIC® patches are intended for transdermal use (on intact skin) only. Using damaged DURAGESIC® patches can lead to the rapid release and absorption of a potentially fatal dose of fentanyl . In addition, exposure to the contents of a DURAGESIC® patch can lead to potentially fatal respiratory depression.

DURAGESIC® is ONLY for use in patients who are already tolerant to opioid therapy of comparable potency. Use in non-opioid tolerant patients may lead to fatal respiratory depression. Overestimating the DURAGESIC® dose when converting patients from another opioid medication can result in fatal overdose with the first dose. Due to the mean elimination half-life of 17 hours of DURAGESIC®, patients who are thought to have had a serious adverse event, including overdose, will require monitoring and treatment for at least 24 hours.

The concomitant use of DURAGESIC® with potent cytochrome P450 3A4 inhibitors (ritonavir, ketoconazole, itraconazole, troleandomycin, clarithromycin, nelfinavir, and nefazodone) may result in an increase in fentanyl plasma concentrations, which could increase or prolong adverse drug effects and may cause potentially fatal respiratory depression. Patients receiving DURAGESIC® and potent CYP3A4 inhibitors should be carefully monitored for an extended period of time and dosage adjustments should be made if warranted. (See BOX WARNING, WARNINGS, CLINICAL PHARMACOLOGY – Drug Interactions and PRECAUTIONS for further information.)

General Principles
DURAGESIC® is indicated for management of persistent, moderate to severe chronic pain that:

- **requires continuous, around-the-clock opioid administration for an extended period of time**
- **cannot be managed by other means such as non-steroidal analgesics, opioid combination products, or immediate-release opioids**

DURAGESIC® should ONLY be used in patients who are already receiving opioid therapy, who have demonstrated opioid tolerance, and who require a total daily dose at least equivalent to DURAGESIC® 25 mcg/h. Patients who are considered opioid-tolerant are those who have been taking, for a week or longer, at least 60 mg of morphine daily, or at least 30 mg of oral oxycodone daily, or at least 8 mg oral hydromorphone daily, or an equianalgesic dose of another opioid.

Because serious or life-threatening hypoventilation could occur, DURAGESIC® (fentanyl transdermal system) is contraindicated:

- **in patients who are not opioid-tolerant**
- **in the management of acute pain or in patients who require opioid analgesia for a short period of time.**
- **in the management of post-operative pain, including use after out-patient or day surgeries (e.g., tonsillectomies)**
- **in the management of mild pain**
- **in the management of intermittent pain (e.g., use on an as needed basis [prn])**

(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 2 years of age or older (see PRECAUTIONS - Pediatric Use).

Prescribers should individualize treatment using a progressive plan of pain management such as outlined by the World Health Organization, the Agency for Health Research and Quality, the Federation of State Medical Boards Model Policy, or the American Pain Society.

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 intact, non-irritated, and non-irradiated skin on a flat surface such as the chest, back, flank, or upper arm. In young children and persons with cognitive impairment, adhesion should be monitored and the upper back is the preferred location to minimize the potential of inappropriate patch removal. 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 patch, 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 patch application.

DURAGESIC® should be applied immediately upon removal from the sealed package. Do not use if the seal is broken. Do not alter the patch (e.g., cut) in any way prior to application and do not use cut or damaged patches.

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. If the gel

from the drug reservoir accidentally contacts the skin of the patient or caregiver, the skin 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.

Each DURAGESIC® may be worn continuously for 72 hours. The next patch 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 patches should be folded so that the adhesive side of the patch adheres to itself, then the patch should be flushed down the toilet immediately upon removal. Patients should dispose of any patches remaining from a prescription as soon as they are no longer needed. Unused patches should be removed from their pouches, folded so that the adhesive side of the patch adheres to itself, 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® is ONLY for use in patients who are already tolerant to opioid therapy of comparable potency. Use in non-opioid tolerant patients may lead to fatal respiratory depression.

Pediatric patients converting to DURAGESIC® therapy with a 25 mcg/h patch should be opioid-tolerant and receiving at least 60 mg of oral morphine equivalents per day. The dose conversion schedule described in Table C and method of titration described below are recommended in opioid-tolerant pediatric patients over 2 years of age 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 (e.g., 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 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

Overestimating the DURAGESIC® dose when converting patients from another opioid medication can result in fatal overdose with the first dose. Due to the mean

elimination half-life of 17 hours of DURAGESIC®, patients who are thought to have had a serious adverse event, including overdose, will require monitoring and treatment for at least 24 hours.

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. The efficacy of DURAGESIC® 12 mcg/h as an initiating dose has not been determined. In addition, patients who are not opioid-tolerant have experienced hypoventilation and death during use of DURAGESIC®. Therefore, DURAGESIC® should be used only in patients who are opioid-tolerant.

To convert adult and pediatric patients from oral or parenteral opioids to DURAGESIC®, use Table C:

Alternatively, for adult and pediatric patients taking opioids or doses not listed in Table C, use the following methodology:

1. Calculate the previous 24-hour analgesic requirement.
2. Convert this amount to the equianalgesic oral morphine dose using Table D.
3. Table E 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 mcg/h, multiple systems may be used.

TABLE C[1]
DOSE CONVERSION GUIDELINES

Current Analgesic	Daily Dosage (mg/d)			
Oral morphine	60-134	135-224	225-314	315-404
IM/IV morphine	10-22	23-37	38-52	53-67
Oral oxycodone	30-67	67.5-112	112.5-157	157.5-202
IM/IV oxycodone	15-33	33.1-56	56.1-78	78.1-101
Oral codeine	150-447	448-747	748-1047	1048-1347
Oral hydromorphone	8-17	17.1-28	28.1-39	39.1-51
IV hydromorphone	1.5-3.4	3.5-5.6	5.7-7.9	8-10
IM meperidine	75-165	166-278	279-390	391-503
Oral methadone	20-44	45-74	75-104	105-134
IM methadone	10-22	23-37	38-52	53-67
	⇓	⇓	⇓	⇓
Recommended DURAGESIC® Dose	25 mcg/h	50 mcg/h	75 mcg/h	100 mcg/h

Alternatively, for adult and pediatric patients taking opioids or doses not listed in Table C, use the conversion methodology outlined above with Table D.

[1]Table C should not be used to convert from DURAGESIC® to other therapies because this conversion to DURAGESIC® is conservative. Use of table C 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®).

TABLE D[a]
EQUIANALGESIC POTENCY CONVERSION

Name	Equianalgesic Dose (mg) IMb,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

[1]Table D 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®).

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 Cmax and Tmax.

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

Oral 24-hour Morphine (mg/day)	DURAGESIC® Dose (mcg/h)
60-134[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]Table E should not be used to convert from DURAGESIC® to other therapies because this conversion to DURAGESIC® is conservative. Use of table E 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 mcg/h DURAGESIC® system should be opioid-tolerant and receiving at least 60 mg oral morphine equivalents per day.

The majority of patients are adequately maintained with DURAGESIC® administered every 72 hours. Some 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® dose may be increased after 3 days (see DOSAGE AND ADMINISTRATION - 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® dose may be increased after 3 days based on the daily dose of supplemental opioid 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 45 mg/24 hours of oral morphine to a 12.5 mcg/h increase in DURAGESIC® dose. DURAGESIC®-12 delivers 12.5 mcg/h of fentanyl.

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.

Tables C, D, and E should not be used to convert from DURAGESIC® to other therapies. Because the conversion to DURAGESIC® is conservative, use of tables C, D, and E 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 (mcg/h)	System Size (cm2)	Fentanyl Content (mg)	NDC Number
DURAGESIC®-12	5	1.25	50458-037-05
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

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, which can lead to the rapid release and absorption of a potentially fatal dose of fentanyl.

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

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

A schedule CII narcotic. DEA order form required.

Manufactured by:
ALZA Corporation
Mountain View, CA 94043

Distributed by:
Janssen Pharmaceutica Products, L.P
Titusville, NJ 08560

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®?

- **DURAGESIC® contains fentanyl, a strong opioid narcotic pain medicine. DURAGESIC® can cause serious side effects, including trouble breathing, which can be fatal, especially if used the wrong way.**

- **DURAGESIC® is only for patients with chronic (around the clock) pain that is moderate to severe and expected to last for weeks or longer. DURAGESIC® should only be started if you are already using other opioid narcotic medicines.**

- **DURAGESIC® is not for patients who need opioid pain medicines for only a short time.** This includes the pain that happens with surgery (such as tonsillectomies), medical, or dental procedures (such as wisdom tooth removal).

- **DURAGESIC® is not for occasional ("as needed") use.**

- **You should NOT use DURAGESIC® unless you are opioid tolerant. You are opioid tolerant if you have been taking at least 60 milligrams (mg) of oral morphine daily, or at least 30 mg of oral oxycodone daily, or at least 8 mg of oral hydromorphone daily, or an equally strong dose of another opioid for a week or longer before starting DURAGESIC®. If you are unsure if you are opioid-tolerant, discuss this with your health care provider.**

- **DURAGESIC® is only for adults and children 2 years of age or older who have already been using opioid narcotic pain medicines for a week or more. Children should ONLY use DURAGESIC® if they have been taking at least 60 milligrams (mg) of oral morphine daily or at least 30 mg of oral oxycodone daily or at least 8 mg oral hydromorphone daily or an equally strong dose of another opioid for a week or longer before starting DURAGESIC®.**

- **Do not use the DURAGESIC® patch if the seal is broken or the patch is cut, damaged or changed in any way. Using a patch that is cut, damaged, or changed in any way can expose you to the contents of the patch, which contains a potentially fatal dose of medicine.**

- **Keep DURAGESIC® in a safe place away from children.** Accidental use by a child is a medical emergency and can result in death. If a child accidentally is exposed to a **DURAGESIC®** patch, call your local Poison Control Center or the nearest emergency room right away.

- **DURAGESIC® is an opioid (narcotic) pain medicine.** There is a chance you could get addicted to **DURAGESIC®**. The chance is higher if you are or have been addicted to or abused other medicines, street drugs, or alcohol, or if you have a history of mental problems.

- Keep your **DURAGESIC®** in a safe place to protect it from being stolen since it can be a target for people who abuse narcotic medicines or street drugs. Never give **DURAGESIC®** to anyone else, even if they have the same symptoms you have. It may harm them and cause death. Selling or giving away this medicine is against the law.

- **Some medicines may cause serious or life-threatening side effects when used with DURAGESIC®. Talk to your health care provider about all the medicines you are taking.**

What is DURAGESIC®?

DURAGESIC® is a prescription medicine that contains fentanyl. DURAGESIC® is a federally controlled substance (CII) because it is a strong opioid narcotic pain medicine that can be abused by people who abuse prescription medicines or street drugs.

DURAGESIC® is only for patients with chronic (around the clock) pain that is moderate to severe and expected to last for weeks or longer.

You should ONLY use DURAGESIC® if you have been taking at least 60 milligrams (mg) of oral morphine daily, or at least 30 mg of oral oxycodone daily, or at least 8 mg of oral hydromorphone daily, or an equally strong dose of another opioid for a week or longer before starting DURAGESIC®.

DURAGESIC® is not for patients who need opioid pain medicines for only a short time. This includes the pain that happens with surgery (such as tonsillectomies), medical, or dental procedures (such as wisdom tooth removal).

DURAGESIC® is not for occasional ("as needed") use.

DURAGESIC® should not be the first opioid (narcotic) pain medicine that is prescribed for your pain.

DURAGESIC® is only for opioid tolerant children 2 years of age or older who are already using other opioid narcotic pain medicines. Pediatric patients 2 years of age or older are opioid tolerant if they are taking at least 60 milligrams (mg) of oral morphine daily, or at least 30 mg of oral oxycodone daily, or at least 8 mg of oral hydromorphone daily, or an equally strong dose of another opioid for a week or longer before starting DURAGESIC®.

Who should not use DURAGESIC®?

Do not use DURAGESIC®:

- **If you are NOT already using other opioid narcotic medicines**
- If you need opioid pain medicines for only a short time
- For pain from surgery, medical or dental procedures
- If your pain can be taken care of by occasional use of other pain medicines.
- In children who are less than 2 years of age
- In children 2 years of age or older who are not already using other opioid narcotic pain medicines (opioid tolerant).
- If you have acute (sudden) or severe asthma
- If you have a gastrointestinal problem called paralytic ileus
- If you are allergic to any of the ingredients in DURAGESIC®.

What should I tell my health care provider before starting DURAGESIC®?

Tell your health care provider about all of your medical problems,

especially if you have:

- **trouble breathing or lung problems** such as asthma, wheezing, or shortness of breath
- **a head injury or brain problems**
- **a heart problem called bradycardia (slow heart beat)**
- **liver or kidney problems**
- seizures (convulsions or fits)
- gallbladder problems
- low thyroid (hypothyroidism)

- low blood pressure
- problems urinating
- major depression
- hallucinations (seeing or hearing things that are not seen by other people)
- adrenal gland problems such as Addison's disease
- a past or present drinking problem or alcoholism, or a family history of this problem
- a past or present drug abuse or addiction problem, or a family history of this problem
- **Have skin reactions to the adhesives (glues) used in** DURAGESIC®. See the end of this leaflet for a complete list of all the ingredients in 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.

Some medicines may cause serious or life-threatening 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. Be especially careful about other medicines that make you sleepy such as other pain medicines, sleeping pills, anxiety medicines, antihistamines, or tranquilizers.

Do not start any new prescription medicine, non-prescription medicine, or herbal supplement while using DURAGESIC® until you have talked to your healthcare provider. Your healthcare provider will tell you if it is safe to take other medicines while you are using DURAGESIC®.

What should I know about using DURAGESIC® in children?

DURAGESIC® can be used in children 2 years of age or older only if they are already using other opioid narcotic pain medicines for a week or more. Children should ONLY use DURAGESIC® if they have been taking at least 60 milligrams (mg) of oral morphine daily, or at least 30 mg of oral oxycodone daily, or at least 8 mg of oral hydromorphone daily, or an equally strong dose of another opioid for a week or longer before starting DURAGESIC®.

When DURAGESIC ® is used in young children; put the patch on the child's upper back. This will lower the chances that the child will remove the patch and put it in their mouth.

Keep DURAGESIC® in a safe place. Keep DURAGESIC® out of the reach of children. **Accidental use in children is a medical emergency and can result in death. If a child accidentally takes DURAGESIC®, call your local Poison Control Center or go to the nearest emergency room right away.**

How do I use DURAGESIC®?

- Follow your health care provider's directions exactly. Your health care provider may change your dose after seeing how the medicine affects you.
- **Do not use the DURAGESIC® patch if the seal is broken or the patch is cut, damaged or changed in any way. Using a patch that is cut, damaged, or changed in any way can expose you to the contents of the patch, which contains a potentially fatal dose of 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 more DURAGESIC® than your health care provider has prescribed or overdose, get emergency medical help right away.
- If you have concerns about abuse or addiction when using your pain medicine or if you have experienced drug or alcohol abuse or addiction in the past, or have a family history of these problems, 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. (See "What should I avoid while using DURAGESIC®")

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 be released at once and this can be dangerous.

- **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®**. If your healthcare provider decides you no longer need DURAGESIC®, ask how to slowly reduce this medicine so you don't have withdrawal symptoms. **Do not stop taking DURAGESIC® without talking to your healthcare provider.** Stopping DURAGESIC® suddenly can make you sick with withdrawal symptoms.

- **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.**

What are the possible side effects of DURAGESIC®?

- **DURAGESIC® can cause serious side effects, including trouble breathing, which can be fatal, especially if used the wrong way. See "What is the most important information I should know about DURAGESIC®?"**

Call your healthcare provider right away or get emergency medical help if you:

- Have trouble breathing
- Have extreme drowsiness with slowed breathing

- Have shortness of breath (little chest movement with breathing)
- Feel faint, dizzy, confused, or have other unusual symptoms

These can be symptoms that you have taken too much (overdose) DURAGESIC® or the dose is too high for you. These symptoms may lead to serious problems or death if not treated right away.

Some medicines may cause serious or life-threatening side effects when used with DURAGESIC®. Talk to your health care provider about all the medicines you are taking.

You can develop physical dependence on DURAGESIC®. Stopping DURAGESIC® suddenly can make you sick with withdrawal symptoms. Talk to your healthcare provider about slowly stopping DURAGESIC®.

There is a chance you could get addicted to DURAGESIC®. The chance is higher if you are or have been addicted to or abused other medicines, street drugs, or alcohol, or if you have a history of mental problems.

DURAGESIC® can cause your blood pressure to drop. This can make you feel dizzy if you get up too fast from sitting or lying down.

The 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.

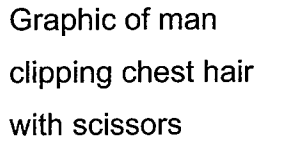
Constipation (less frequent than usual or hard bowel movements) is a very common side effect of opioids including DURAGESIC® and is unlikely to go away without treatment. Talk to your healthcare provider about the use of laxatives (medicines to treat constipation) and stool softeners to prevent or treat constipation while taking DURAGESIC®.

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

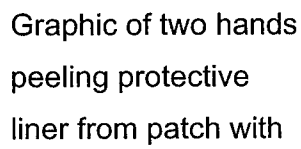
How and where to apply DURAGESIC®

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 and people who have impaired thinking, put the patch on the upper back. This will lower the chances that the patch will be removed

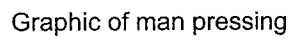
1. **Prepare:** For adults, put the patch on the chest, back, flank (sides of the waist), or upper arm in a place where there is no hair. Put it on right away after you have removed it from the pouch and after you have removed the protective liner. Avoid sensitive areas or those that move around a lot.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


Graphic of man clipping chest hair with scissors

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® is a patch with a drug-containing gel sealed inside. This design keeps 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 use the DURAGESIC® patch if the seal is broken or the patch is cut, damaged or changed in any way. Using a patch that is cut, damaged, or changed in any way can expose you to the contents of the patch, which contains potentially fatal dose of medicine.

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, wash the area with water, and seek immediate medical attention. Call a health care provider or poison control center.

Prevent theft and misuse. DURAGESIC® contains an opioid 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.

Keep DURAGESIC ® in a safe place. Keep DURAGESIC® out of the reach of children. **Accidental use in children is a medical emergency and can result in death. If a child accidentally takes DURAGESIC®, call your local Poison Control Center or get emergency medical help right away.**

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. **DURAGESIC® can harm other people and even cause death. Sharing DURAGESIC® is against the law.**

Keep DURAGESIC® out of the reach of children and pets. Accidental use in children and pets is a medical emergency and can result in death. If a child

or pet accidentally takes DURAGESIC®, call your local Poison Control Center or get emergency medical help right away.

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

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-813 / S - 039

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA 19-813
Submission Number	039
Submission Code	SE2
Letter Date	April 5 2004
Stamp Date	April 5 2004
PDUFA Goal Date	February 5 2005
Reviewer Name	D. Elizabeth McNeil MD
Review Completion Date	December 30 2004
Established Name	Fentanyl Transdermal System
(Proposed) Trade Name	Duragesic
Therapeutic Class	Analgesic
Applicant	ALZA
Priority Designation	S
Formulation	Transdermal system
Dosing Regimen	One system every 72 hours
Indication	Moderate to severe pain
Intended Population	Opioid tolerant persons

Table of Contents

1 EXECUTIVE SUMMARY 5

1.1 RECOMMENDATION ON REGULATORY ACTION 5
1.2 RECOMMENDATION ON POSTMARKETING ACTIONS 5
1.2.1 Risk Management Activity 5
1.2.2 Required Phase 4 Commitments 5
1.2.3 Other Phase 4 Requests 5
1.3 SUMMARY OF CLINICAL FINDINGS 6
1.3.1 Brief Overview of Clinical Program 6
1.3.2 Efficacy 6
1.3.3 Safety 6
1.3.4 Dosing Regimen and Administration 7
1.3.5 Drug-Drug Interactions 7
1.3.6 Special Populations 7

2 INTRODUCTION AND BACKGROUND 9

2.1 PRODUCT INFORMATION 9
2.2 CURRENTLY AVAILABLE TREATMENT FOR INDICATIONS 9
2.3 AVAILABILITY OF PROPOSED ACTIVE INGREDIENT IN THE UNITED STATES 9
2.4 IMPORTANT ISSUES WITH PHARMACOLOGICALLY RELATED PRODUCTS 10
2.5 PRESUBMISSION REGULATORY ACTIVITY 10
2.6 OTHER RELEVANT BACKGROUND INFORMATION 10

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES 10

3.1 CMC (AND PRODUCT MICROBIOLOGY, IF APPLICABLE) 10
3.2 ANIMAL PHARMACOLOGY/TOXICOLOGY 10

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY 11

4.1 SOURCES OF CLINICAL DATA 11
4.2 TABLES OF CLINICAL STUDIES 11
4.3 REVIEW STRATEGY 11
4.4 DATA QUALITY AND INTEGRITY 12
4.5 COMPLIANCE WITH GOOD CLINICAL PRACTICES 12
4.6 FINANCIAL DISCLOSURES 12

5 CLINICAL PHARMACOLOGY 12

5.1 PHARMACOKINETICS 12
5.2 PHARMACODYNAMICS 13
5.3 EXPOSURE-RESPONSE RELATIONSHIPS 13

6 INTEGRATED REVIEW OF EFFICACY 13

6.1 INDICATION 13
6.1.1 Methods 14
6.1.2 General Discussion of Endpoints 14
6.1.3 Study Design 14
6.1.4 Efficacy Findings 14
6.1.5 Clinical Microbiology 14
6.1.6 Efficacy Conclusions 14

7 INTEGRATED REVIEW OF SAFETY 14

7.1 METHODS AND FINDINGS 14
7.1.1 Deaths 14

7.1.2 Other Serious Adverse Events 14
7.1.3 Dropouts and Other Significant Adverse Events 16
7.1.4 Other Search Strategies 19
7.1.5 Common Adverse Events 19
7.1.6 Less Common Adverse Events 23
7.1.7 Laboratory Findings 23
7.1.8 Vital Signs 24
7.1.9 Electrocardiograms (ECGs) 24
7.1.10 Immunogenicity 25
7.1.11 Human Carcinogenicity 25
7.1.12 Special Safety Studies 25
7.1.13 Withdrawal Phenomena and/or Abuse Potential 25
7.1.14 Human Reproduction and Pregnancy Data 25
7.1.15 Assessment of Effect on Growth 26
7.1.16 Overdose Experience 26
7.1.17 Postmarketing Experience 26
7.2 ADEQUACY OF PATIENT EXPOSURE AND SAFETY ASSESSMENTS 27
7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety 27
7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety 28
7.2.3 Adequacy of Overall Clinical Experience 28
7.2.4 Adequacy of Special Animal and/or In Vitro Testing 28
7.2.5 Adequacy of Routine Clinical Testing 28
7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup 29
7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study 29
7.2.8 Assessment of Quality and Completeness of Data 29
7.2.9 Additional Submissions, Including Safety Update 29
7.3 SUMMARY OF SELECTED DRUG-RELATED ADVERSE EVENTS, IMPORTANT LIMITATIONS OF DATA, AND CONCLUSIONS 29
7.4 GENERAL METHODOLOGY 30
7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence 30
7.4.2 Explorations for Predictive Factors 30
7.4.3 Causality Determination 30

8 ADDITIONAL CLINICAL ISSUES 31

8.1 DOSING REGIMEN AND ADMINISTRATION 31
8.2 DRUG-DRUG INTERACTIONS 31
8.3 SPECIAL POPULATIONS 31
8.4 PEDIATRICS 31
8.5 ADVISORY COMMITTEE MEETING 32
8.6 LITERATURE REVIEW 32
8.7 POSTMARKETING RISK MANAGEMENT PLAN 32
8.8 OTHER RELEVANT MATERIALS 33

9 OVERALL ASSESSMENT 33

9.1 CONCLUSIONS 33
9.2 RECOMMENDATION ON REGULATORY ACTION 33
9.3 RECOMMENDATION ON POSTMARKETING ACTIONS 33
9.3.1 Risk Management Activity 33
9.3.2 Required Phase 4 Commitments 33
9.3.3 Other Phase 4 Requests 34
9.4 LABELING REVIEW 34
9.5 COMMENTS TO APPLICANT 35

10 APPENDICES 37

10.1 REVIEW OF INDIVIDUAL STUDY REPORTS 37
10.2 LINE-BY-LINE LABELING REVIEW 45

1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

I recommend approval of the Duragesic 12 mcg transdermal system as a titration step between the currently marketed Duragesic dosage strengths: 25 mcg/hr, 50 mcg/hr, 75 mcg/hr, 100 mcg/hr.

The Duragesic 12 mcg/hr system has been shown to have no clinically significant safety issues that are not already seen in the marketed dosage strengths. The most common adverse events are headache, nausea and vomiting. The most worrisome side effect with Duragesic and opioids in general is respiratory depression. Though no instances of respiratory depression were seen during the trials with Duragesic 12 mcg/hr, the concern remains because of the prolonged half-life of the drug due to the skin-depot effect associated with transdermal administration of fentanyl.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

ALZA has expressed concern that fentanyl abuse may be a growing problem in the American market (citizen's petition dated 24 November 2004, Docket # # 2004P-0506). The Division of Anesthetic, Critical Care and Addiction Drug Products (DACCADP), shares this concern. In light of the material submitted by ALZA on the potential for abuse of the transdermal fentanyl system, as well as proprietary information on fentanyl abuse provided to us by the Agency's Controlled Substances Staff (CSS), we agree that a risk management plan (RMP) may be warranted to address concerns related to the abuse, misuse and diversion of gel-in-reservoir fentanyl transdermal systems such as Duragesic. DACCADP, along with CSS and the Office of Drug Safety (ODS), would support ALZA's efforts to devise such a plan.

1.2.2 Required Phase 4 Commitments

There are no required Phase 4 commitments for this application.

1.2.3 Other Phase 4 Requests

There are no other Phase 4 requests for this submission.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

Fentanyl is a synthetic phenylpiperidine opioid agonist. Duragesic permits transdermal administration of fentanyl with a dosing interval of 72 hours. ALZA currently manufactures Duragesic in four dosage strengths (25 mcg/h, 50 mcg/h, 75 mcg/h, 100 mcg/h), all of which are approved for use in persons 2 years old and older who require continuous opioid analgesia. The sponsor wishes to provide an intermediate strength, 12 mcg/h, for use in dose titration.

The sponsor did two new biopharmaceutics trials with the 12 mcg/hr patch in support of this application:

- FEN-GBR-19: A bioequivalence study which compared 4 Duragesic 12-mcg systems to 2 Duragesic 25 mcg systems
- FEN-BEL-9: A clinical pharmacology study designed to evaluate the pharmacokinetics after a single application of a 12 mcg Duragesic system.

The sponsor has performed one uncontrolled safety and clinical utility study in 227 adults with chronic pain: FEN-USA-86. The study results were originally submitted to the Duragesic IND (IND 24, 417, sN104) and were provided as part of this sNDA submission upon Agency request. The sponsor has performed three uncontrolled safety and clinical utility studies in the pediatric population: FEN-USA-87; FEN-INT-24; and FEN-GBR-14. The safety and efficacy information from those three studies was reviewed as part of N19-813, sN 036.

1.3.2 Efficacy

FEN-USA-86, FEN-BEL-9 and FEN-GBR-19 were uncontrolled safety and clinical utility studies. In the absence of an appropriately controlled double-blind study, no definitive comments can be made about the efficacy of the 12 mcg system as a stand-alone dose.

1.3.3 Safety

During the development plan, a total of 267 people were exposed to the Duragesic 12 mcg system for a period ranging from 72 hours to 28 days. Although Duragesic 12 was studied in opioid naïve patients, they were noted to have a higher incidence of some of the more common adverse events than opioid-exposed individuals. Duragesic, at any dosage, is not indicated for use in opioid naïve individuals.

Duragesic, in higher strengths, has been marketed since 1990 so extensive postmarketing data is available. The Duragesic 12 mcg/hr system has a similar adverse event profile to the currently marketed Duragesic systems. The most common adverse events are nausea, vomiting and headache. The most dangerous adverse event is respiratory depression. Hypoventilation leading to death has been reported in patients given Duragesic for the management of acute pain, for

example fractures or post-operative pain, such as third molar extractions, tonsillectomies. The boxed warning for this product lists both acute pain and postoperative use as contraindications

The current Duragesic labeling notes that fentanyl is associated with impaired fertility and embryocidal effects in rats when given at intravenous doses 0.3 times the human dose for 12 days. There is no evidence of teratogenic effects in rodents. Duragesic is currently considered pregnancy category C. There is no data from adequate and well-controlled studies on the use of Duragesic in pregnant women. Fentanyl is known to be excreted in human breast milk, therefore it is not recommended for use in nursing women.

Opiates are known to have abuse potential. The proposed 12 mcg Duragesic system does not have an abuse potential that differs from the currently marketed transdermal fentanyl products.

1.3.4 Dosing Regimen and Administration

This product, Duragesic 12mcg/hr, is designed for use in dose titration between the currently marketed dosage strengths: 25 mcg/h, 50 mcg/h, 75 mcg/h, 100 mcg/h.

1.3.5 Drug-Drug Interactions

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 significantly reduced.

Since the metabolism of fentanyl is mediated by the CYP3A4 isoenzyme, coadministration of drugs that inhibit CYP3A4 activity may cause decreased clearance of fentanyl. The expected clinical results would be increased or prolonged opioid effects. Cytochrome P450 inducers, such as rifampin, carbamazepine, and phenytoin, induce metabolism and as such may cause increased clearance of fentanyl.

Fentanyl may be expected to have additive effects when used in conjunction with alcohol, other opioids, or illicit drugs that cause central nervous system depression.

1.3.6 Special Populations

Pediatrics
Duragesic in the currently marketed 25, 50, 75, and 100 mcg strengths has been approved for administration to opioid-tolerant children aged 2 years and older. The currently proposed 12 mcg/hr dosage system should be made available for dose titration in opioid-tolerant children using Duragesic for analgesia.

Concomitant medical conditions

The sponsor did not perform studies in special populations for this application. The following information comes verbatim from the approved labeling for Duragesic:

> "Because potent opioids can cause hypoventilation, DURAGESIC® 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.
>
> DURAGESIC® should not be used in patients who may be particularly susceptible to the intracranial effects of CO2 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.
>
> Fentanyl may produce bradycardia. Fentanyl should be administered with caution to patients with bradyarrhythmias.
>
> 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."

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Duragesic (fentanyl transdermal patch, NDA 19-813), a synthetic phenylpiperidine opioid agonist, was approved in 1990 for the management of chronic pain in patients requiring continuous opioid analgesia.

Duragesic, a gel-in-reservoir system, permits transdermal administration of fentanyl with a dosing interval of 72 hours. Opioids have distinct effects on the central nervous system and may cause miosis, increased parasympathetic activity and/or sedation. 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. The most serious risk associated with fentanyl use is respiratory depression.

The sponsor currently manufactures Duragesic in four dosage strengths (25 mcg/h, 50 mcg/h, 75 mcg/h, 100 mcg/h), all of which are approved for use in persons 2 years old and older. The sponsor wishes to provide an intermediate strength, 12 mcg/h system, for use in dose titration. The sponsor is not requesting a change in indication.

The sponsor is proposing that approval of this product be based upon dose proportionality to the currently approved and marketed 25 mcg strength Duragesic system.

2.2 Currently Available Treatment for Indications

Fentanyl is currently available in the US as an injectable formulation, as a transdermal patch, and as an oral lozenge. Various formulations of morphine, hydromorphone, and oxycodone products are marketed for use in patients with chronic pain requiring continuous opioid analgesia.

2.3 Availability of Proposed Active Ingredient in the United States

Duragesic contains fentanyl gel in a drug reservoir. In early 2004, a Class I recall of five lots of the Duragesic 75 mcg strength product was instituted due to the discovery of a manufacturing defect leading to leakage of the fentanyl gel from an incompletely sealed edge of the system. ALZA has instituted enhanced quality control/assurance systems to reduce the risk of a recurrence of this occurrence.

The oral transmucosal fentanyl formulation (lozenge)is currently marketed under Subpart H due to safety concerns since it represents a potent opioid marketed in a form that may be mistaken for a lollipop or another form of candy.

2.4 Important Issues With Pharmacologically Related Products

In light of safety issues that have arisen concerning determinations of appropriate patients for use of opioid containing products, a standard sentence defining what should be considered an "opioid tolerant patient" will be added to the label for all opioid containing products. This sentence, which will be modified as appropriate to reflect current knowledge, has already been incorporated into the oral transmucosal fentanyl (e.g. ACTIQ) and the hydromorphone hydrochloride (e.g. Palladone) labels.

2.5 Presubmission Regulatory Activity

ALZA submitted NDA 19-813 supplement number 036 to gain approval for use of Duragesic in the pediatric population. Those studies used a 12.5 mcg investigational system for initiation of therapy in some patients. During review of that supplement, the Division recommended that if ALZA chose to go forward with development of a 12.5 mcg strength, that system should be made distinctive to reduce the risk for confusion with a possible 125 mcg dosage.

The sponsor has created a system with an active area equal to 5 square centimeters, half that of the currently marketed 25 mcg/h system. While this system provides a nominal dose of 12.5 mcg/hr, the delivery is referred to as 12 mcg/h. In discussions with the Division, ALZA was told that it would be acceptable to refer to the system in this manner since doing so would reduce the risk of prescriber and/or dispensing confusion between 12.5 mcg and 125 mcg.

2.6 Other Relevant Background Information

None

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

Based on preliminary discussion with the CMC reviewer, ALZA has provided acceptable product stability data for 36 months though the requested expiration date is 12 months. There were no clinically significant issues.

[Reviewer's note: Details of the CMC issues may be found in the review of this submission done by Dr. Jila Boal of the Office on New Drug Chemistry.]

3.2 Animal Pharmacology/Toxicology

There was no new animal pharmacology/toxicology data submitted with this application.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The sponsor did two new biopharmaceutics trials with the 12 mcg/hr patch in support of this application:

- FEN-GBR-19: A bioequivalence study which compared 4 Duragesic 12-mcg systems to 2 Duragesic 25 mcg systems
- FEN-BEL-9: A clinical pharmacology study designed to evaluate the pharmacokinetics after a single application of a 12 mcg Duragesic system.

The sponsor performed one uncontrolled safety and clinical utility study in adults with chronic pain: FEN-USA-86. This study was submitted to the IND for this product (IND 24, 417, sN104) and initially was only summarized as part of this application. At the Division's request, the data from that study was submitted to this sNDA as well. The safety data from this clinical study will be reviewed in full along with the safety data from the aforementioned biopharmaceutics studies.

[Reviewer's note: A protocol review of study FEN-USA-86 has been provided in Appendix A. Details of the biopharmaceutics studies may be found in the review of this submission done by Dr. Sue-Chih Lee of Biopharmaceutics.]

The sponsor performed three uncontrolled safety and clinical utility studies in the pediatric population: FEN-USA-87; FEN-INT-24; and FEN-GBR-14. The safety and efficacy information from those three studies was reviewed as part of N19-813, sN 036 and will not be the subject of detailed discussion in this application.

4.2 Tables of Clinical Studies

Table 1: Table of clinical studies

	Study type	Number of subjects	Study Duration
FEN-GBR-19	Bioequivalence	33 enrolled, 32 completed	72 hours
FEN-BEL-9	Pharmacokinetics	8 enrolled, 8 completed	5 days
FEN-USA-86	Open-label safety	227 enrolled, 194 completed	28 days

4.3 Review Strategy

The only data sources for this review were the currently submitted data and the pediatric data previously submitted to this NDA in sN036.

All three trials listed in the table above, section 4.2, were evaluated for safety. While study FEN-USA-86 was done in a population of patients with chronic pain, it was done as an open-label

study to demonstrate safety and clinical utility and was not designed to support an efficacy claim for the 12 mcg system.

All of the electronic submissions to sN039 were reviewed in whole or in part. The study protocols, study reports and study results were reviewed for FEN-USA-86 and the other two supporting studies.

The ISS was reviewed in depth. The data in the tables was compared with the data in the appendices. Each serious adverse event (SAE) 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. According to the sponsor, Site 16 in study FEN-USA-86 was found to have poor source documentation with unverifiable information and unresolvable discrepancies so the efficacy results from that site were excluded. The safety information from patients enrolled at that site (n=14) was reviewed in depth.

4.4 Data Quality and Integrity

The site where the primary bioequivalence study (FEN-GBR-19) was performed had been inspected by DSI close to the time that the study was performed.

The Division did not request an audit by the Division of Scientific Investigations nor was one done for this review.

4.5 Compliance with Good Clinical Practices

The trials were conducted in accordance with accepted ethical standards.

4.6 Financial Disclosures

The sponsor has provided financial information from an investigator, Dr. Norma Watson, in study FEN-GBR-19. That data revealed no potential conflict of interest.

On October 25, 2004, ALZA was contacted to ask about financial disclosure information for the investigators on the other studies. On December 27 2004, a repeat request was sent.

5 CLINICAL PHARMACOLOGY

5.1 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. The principal clinical effects are referable to the central nervous system, where fentanyl 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 measurable serum concentration of fentanyl 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, a skin depot effect associated with transdermal administration of fentanyl. 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 presence of age related differences in clearance was evaluated by the Biopharmaceutics reviewer as part of submission 036 to this NDA. In children, 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. (NDA 19-813 submission 036, Volume 231.2, page 10) "

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

5.2 Pharmacodynamics

The sponsor states that "pharmacodynamics were not evaluated as part of this clinical program", therefore there is no data available for review.

5.3 Exposure-Response Relationships

This section is not applicable for this efficacy supplement.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

Duragesic is currently indicated for the management of chronic pain in patients who require continuous analgesia other than non-steroidal analgesics or acetaminophen-opioid combinations.

6.1.1 Methods

All three studies were uncontrolled safety and clinical utility studies.

6.1.2 General Discussion of Endpoints

These open-label studies used pain intensity scores and global measures to evaluate the clinical utility of this product for analgesic use.

6.1.3 Study Design

These were all open-label, uncontrolled safety and clinical utility studies.

6.1.4 Efficacy Findings

These studies were open-label and cannot be used to determine clinical efficacy.

6.1.5 Clinical Microbiology

This section is not applicable for this efficacy supplement.

6.1.6 Efficacy Conclusions

In the absence of an appropriately controlled double-blind study, no definitive comments can be made about the efficacy of the 12 mcg system as a stand-alone dose.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

7.1.1 Deaths

There were no deaths reported for studies FEN-GBR-19, FEN-BEL-9, or FEN-USA-86.

7.1.2 Other Serious Adverse Events

[Reviewer's note: I have noted the adverse events for each patient in bold text]

FEN-BEL-9
There were no SAEs reported for study FEN-BEL-9: A clinical pharmacology study designed to evaluate the pharmacokinetics after a single application of a 12 mcg Duragesic system.

FEN-GBR-19

Three patients were reported to have SAEs during study FEN-GBR-19: A bioequivalence study which compared 4 Duragesic 12-mcg systems to 2 Duragesic 25 mcg systems

- Subject 0028 experienced a severe **headache** after receiving the two 25 mcg systems. This headache began 4 days after dosing and lasted 17 hours. She was given paracetamol as a concomitant medication. This SAE may have been related to study medication but causality cannot be definitively determined.
- Subject 0030 experienced a severe **headache** after receiving the four 12 mcg systems. This headache began 30 minutes after dosing and lasted 8 hours. She was given paracetamol as a concomitant medication. This SAE may have been related to study medication but causality cannot be definitively determined.
- Subject 0032 became **pregnant** during the study. The pregnancy was diagnosed 8 days after she received the two 25 mcg systems and was electively terminated 22 days later. She did not receive the scheduled application of the four 12 mcg systems as she withdrew consent upon detection of her pregnancy. This SAE was not related to study medication.

FEN-USA-86

Seven patients were reported to have SAEs during FEN-USA-86: an uncontrolled safety and clinical utility study in adults with chronic pain.

- Subject A36036 reported **pelvic pain** on study day 20. Two days later she had a bilateral salpingo-oophorectomy as treatment for chronic salpingitis, hydrosalpinx and a hemorrhagic corpus luteum cyst. The Duragesic 12.5 mcg system remained in place during her surgery and subsequent hospital stay. She completed the 28 day trial having started on a 12.5 mcg patch and having increased to a 25 mcg/h patch on study day 13. This SAE was not related to study medication.
- Subject A36063 reported **"flu-like symptoms"** on study day 29 at her termination visit. During the trial she had had three dose increases. She increased to a 25 mcg/h system on study day 4, to 37.5 mcg on study day 16 and to 50 mcg on study day 22. She remained on the latter dose after trial completion. Two weeks after trial completion she was admitted to the hospital as her symptoms continued. While hospitalized she was found to have uncontrolled hypertension and treatment was begun with quinapril. She was discharged after a three day hospitalization. This SAE was not related to study medication.
  [Reviewer's note: This represents a protocol violation at site 16. The maximum allowable dose as per the protocol was 37.5 mcg/hr.]
- Subject A36105 was hospitalized with **right upper lobe pneumonia** on study day 10. The Duragesic 12.5 mcg system remained in place during her hospital stay. She completed the 28 day trial. This SAE may have been related to study medication but causality cannot be definitively determined.
- Subject A36218 reported **nausea, intermittent abdominal cramping, diarrhea, vomiting and diaphoresis** on study day _. She discontinued her 12.5 mcg patch that day. Three days later she was hospitalized for evaluation and treatment of acute gastro-

enteritis and dehydration. This SAE may have been related to study medication but causality cannot be definitively determined.

- Subject A36224 attended an anxiety support group on study day 9. As a result of conversations held there, he became **anxious** about a possible addiction to pain medications. He admitted himself to a chemical dependency unit that day and discontinued his Duragesic 12.5 mcg/hr system. This SAE was not related to study medication.
- Subject A36231 reported **rectal bleeding** 30 days after trial completion. Subsequent evaluation revealed diverticulitis. During the trial she was taking Duragesic 12.5 mcg/hr. At trial completion, she was increased to 25mcg/hr. This SAE was not related to study medication.
- Subject A36243 reported **severe constipation and urinary retention** on stud — He was taken to the hospital for evaluation. There he was diagnosed with uncontrolled **atrial fibrillation**. He was given digoxin, aspirin and diltiazem in the emergency room. The Duragesic 12.5 mcg system remained in place during his hospital stay. He completed the 28 day trial. While the atrial fibrillation was probably not related to study medication, the presenting symptoms of severe constipation and urinary retention may have been related to study medication though causality cannot be definitively determined.

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Overall profile of dropouts

Table 2: Subject disposition [a]

	Disposition	USA-86	BEL-9	GBR-19
Enrolled	268	227	8	33
Completed study treatment period	232 (87%)	194 (85%)	8 (100%)	30 (91%)
Withdrawals	36 (13%)	33 (15%)	0	3 (9%)
Adverse event other than death	24	23	0	1
Withdrew consent	2	1	0	1
Insufficient response	2	2	0	0
Patient noncompliance	2	2	0	0
Ineligible to continue trial	2	1	0	1
Other	4	4	0	0

[a] A full listing of the patients who withdrew from study FEN-USA-86 is provided in Appendix A.

7.1.3.2 Adverse events associated with dropouts

FEN-BEL-9

There were no dropouts reported for study BEL-9.

FEN-GBR-19

There were two dropouts reported for study FEN-GBR-19: subject 31 withdrew consent (no further information is available); subject 32 withdrew consent upon detection of pregnancy. Additionally, one person (subject 18) was enrolled but never received any study drug. He was withdrawn from the study when he fainted during the pre-dose blood sampling.

FEN-USA-86

There were 23 withdrawals due to adverse events reported for this study. The reason for withdrawal is presented in bold text below.

Dropouts during the first 72 hours (3 days) of Duragesic use

- Subject A36013 withdrew from the trial on study day 1 due to **nausea, diaphoresis and tremor.** These symptoms resolved 2 days after the trial medication was stopped. These symptoms may have been related to study medication.
- Subject A36096 withdrew from the trial on study day 1 due to **nausea, lethargy and vertigo**. These symptoms resolved 1 day after the trial medication was stopped. These symptoms may have been related to study medication.
- Subject A36106 withdrew from the trial on study day 1 due to **nausea, vomiting and dizziness**. The vomiting resolved 1 day after the trial medication was stopped. The nausea resolved 3 days after the trial medication was stopped. The dizziness resolved 5 days after the trial medication was stopped. These symptoms may have been related to study medication.
- Subject A36174 withdrew from the trial on study day 3 due to **headache and nausea** which began on study day 1. Both symptoms resolved immediately after the trial medication was stopped. These symptoms may have been related to study medication.
- Subject A36190 withdrew from the trial on study day 1 due to **nausea**. It is not known whether this symptom resolved after the trial medication was stopped. This symptom may have been related to study medication.
- Subject A36218 withdrew from the trial on study day 3 due to **nausea, abdominal pain and diaphoresis**, all of which began on study day 1. The diaphoresis resolved 4 days after the trial medication was stopped. The nausea and abdominal pain resolved 7 days after the trial medication was stopped. These symptoms may have been related to study medication.
- Subject A36225 withdrew from the trial on study day 2 due to **dyspnea, hypertonia, nervousness and urticaria** all of which began on study day 1. The dyspnea resolved immediately after the trial medication was stopped. The urticaria and nervousness resolved 1 day after the trial medication was stopped. These symptoms may have been related to study medication.

Subsequent dropouts

- Subject A36022 withdrew from the trial on study day 6 due to **somnolence**, which began on study day 1. This symptom resolved 14 days after the trial medication was stopped. This symptom may have been related to study medication.

- Subject A36024 withdrew from the trial on study day 18 due to **constipation**, which began on study day 15. This symptom resolved 1 day after the trial medication was stopped. This symptom may have been related to study medication.
- Subject A36123 withdrew from the trial on study day 5 due to **hyperkinesias**, which began on study day 2. This symptom resolved 4 days after the trial medication was stopped. This symptom may have been related to study medication.
- Subject A36157 withdrew from the trial on study day 20 due to **impaired concentration, euphoria, nausea** (all of which began on study day 1) and **fatigue**, which began on study day 14. The impaired concentration, euphoria and nausea resolved 1 day after the trial medication was stopped. The fatigue resolved 3 days after the trial medication was stopped. These symptoms may have been related to study medication.
- Subject A36162 withdrew from the trial on study day 19 due to **dizziness and fatigue** which began on study day 18. Both symptoms resolved 3 days after the trial medication was stopped. These symptoms may have been related to study medication.
- Subject A36164 withdrew from the trial on study day 21 due to **flu-like symptoms** which began on study day 20. These symptoms persisted after the trial medication was stopped. These symptoms may not have been related to study medication.
- Subject A36187 withdrew from the trial on study day 25 due to **headache** which began on study day 24. This symptom resolved 1 day after the trial medication was stopped. This symptom may have been related to study medication.
- Subject A36198 withdrew from the trial on study day 9 due to **nausea and somnolence** which began on study day 8. Both symptoms resolved 1 day after the trial medication was stopped. These symptoms may have been related to study medication.
- Subject A36211 withdrew from the trial on study day 25 due to **impaired concentration, hypertonia, and nausea**, all of which began on study day 25. The nausea resolved immediately after the trial medication was stopped. The impaired concentration and hypertonia resolved 2 days after the trial medication was stopped. These symptoms may have been related to study medication.
- Subject A36212 completed the trial. Two days after trial completion, she was noted to be **confused**. No further information is available. This symptom may have been related to study medication.
- Subject A36215 withdrew from the trial on study day 10 due to **diarrhea and dyspepsia**, which began on study day 4. Both symptoms persisted after the trial medication was stopped. These symptoms may have been related to study medication.
- Subject A36224 has been described in the SAE section (section 7.1.2) and will not be described further.
- Subject A36239 withdrew from the trial on study day 4 due to **nausea** which began on study day 3. The nausea resolved 1 day after the trial medication was stopped. These symptoms may have been related to study medication.
- Subject A36258 withdrew from the trial on study day 14 due to **dizziness** (which began on day 11), **ataxia** which began on study day 12, and **confusion** which also began on study day 12. The confusion resolved 4 days after the trial medication was stopped. The other symptoms resolved five days after the trial medication was stopped. These symptoms may have been related to study medication.

- Subject A36259 withdrew from the trial on study day 7 due to surgical intervention for **carpal tunnel syndrome**. This was not related to study medication.
- Subject A36272 withdrew from the trial on study day 8 due to **fatigue** which began on study day 1. This symptom resolved 2 days after the trial medication was stopped. This symptom may have been related to study medication.
- Subject A36285 withdrew from the trial on study day 16 due to **headache and nausea** which began on study day 1. This symptom resolved immediately after the trial medication was stopped. These symptoms may have been related to study medication.

7.1.3.3 Other significant adverse events

There were no other significant adverse events during these studies that have not already been incorporated into the approved labeling for Duragesic.

7.1.4 Other Search Strategies

No other search strategies were used during the review of this efficacy supplement.

7.1.5 Common Adverse Events

7.1.5.1 Eliciting adverse events data in the development program

Two open-label studies, FEN-GBR-19 and FEN-BEL-9, were performed in naltrexone-blocked healthy volunteers. In both studies, subjects received naltrexone 50 mg every 12 hours beginning the evening before the initiation of Duragesic and ending 12 hours after system removal.

In study FEN-GBR-19, subjects were treated twice as part of a cross-over design. Each treatment comprised 72 hours of Duragesic treatment followed by 48 hours of additional monitoring. A six day washout occurred between study periods. Subjects were queried about adverse events at each trial visit using open-ended quesioning. Respiratory rate was assessed every 15 minutes while the subject was sleeping. Heart rate and blood pressures were obtained at screening and immediately before each blood sample was obtained, i.e. Hour 0, 4, 6, 8, 12, 16, 20, 24, 28, 32, 36, 42, 48, 54, 60, 66, 72, 78, 84, 90, 96, 108, and 120.

In study FEN-BEL-9, subjects were treated with Duragesic once for 72 hours followed by 24 hours of additional monitoring. Queries about adverse events were done with open-ended questions. Respiratory rate was assessed at screening and immediately before each blood sample was obtained, i.e. Hour 0, 4, 6, 8, 12, 16, 20, 24, 28, 32, 36, 42, 48, 54, 60, 66, 72, 78, 84, 90, and 96. Heart rate and blood pressures were obtained at screening at Hour 0, 12, 24, 48, 48, 72, and 96. An electrocardiogram was done at screening.

FEN-USA-86 was a 28-day study performed in opioid-naïve and opioid-experienced patients. Subjects were queried about adverse events using open-ended questioning at each trial visit, i.e study days 1, 2, 4, 7, 10, 13, 16, 19, 22, 25, and 28.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

When the terms used to describe adverse events by the investigators/patients are compared to the preferred terms as categorized by ALZA, the categorization of events appears to have been appropriate.

7.1.5.3 Incidence of common adverse events

The most commonly seen adverse events were headache, nausea and vomiting, all of which are known opioid-related adverse events. The incidences of headache, nausea and vomiting were higher in opioid naïve patients when compared to opioid exposed patients (22% vs. 16%, 33% vs. 18%, and 8% vs. 4% respectively) during study FEN-USA-86. This may reflect the development of a degree of tolerance in the latter group.

Study FEN-GBR-19 was a single dose bioequivalence study in naltrexone blocked healthy volunteers. As may be seen in Table 3 below, the number of enrolled subjects is small, n=31. The incidence of pain and dizziness was higher in the patients who received four 12.5 mcg patches than in those who received two 25 mcg patches. The incidence of headache was higher in the patients who received two 25 mcg patches than in those who received four 12.5 mcg patches. It is difficult to know what, if any, significance those findings have. In any event, headache, pain and dizziness are all currently included in the label as known adverse events with Duragesic use.

Table 3: adverse event table from study FEN-GBR-19 (study report Table I, p. 29)

Adverse events experienced by 2 or more subjects for both treatments by WHO preferred term

Adverse Event, WHO Preferred Term	Number (%) of Subjects with Adverse Events		
	Durogesic patches (Number of Subjects)		
	4 x 12.5 mcg/h (31)	2 x 25 mcg/h (31)	Overall (32)
Headache	4 (12.9%)	6 (19.4%)	9 (28.1%)
Pain	2 (6.5%)	0	2 (6.3%)
Dizziness	3 (9.7%)	0	3 (9.4%)
Nausea	5 (16.1%)	5 (16.1%)	7 (21.9%)
Vomiting	1 (3.2%)	1 (3.2%)	2 (6.3%)
Rash	1 (3.2%)	1 (3.2%)	2 (6.3%)
Rash, erythematous	2 (6.5%)	0	2 (6.3%)
Skin disorder	0	2 (6.5%)	2 (6.3%)

Study FEN-USA-86 was an uncontrolled safety and clinical utility study in adults with chronic pain. In this study patients could receive doses ranging from 12.5 mcg/hr to 37.5 mcg/hr.

Opioid-naïve patients are noted to have had a higher incidence of some of the more common adverse events. A review of the provided adverse events raw data reveals the following:

- 9 complaints of application site reaction among persons with previous opioid exposure as compared to 14 complaints among opioid naïve persons
- 18 complaints of ataxia/dizziness/lightheadedness among persons with previous opioid exposure as compared to 31 complaints among opioid naïve persons
- 26 complaints of headache among persons with previous opioid exposure as compared to 39 complaints among opioid naïve persons

There were other adverse events which were more common in patients with previous opioid exposure. There were 6 complaints of accidental injury, only one of which was opioid-naïve. There were 26 complaints of fatigue/malaise, 11 of whom were opioid naïve. It is unclear why these events occurred in opioid experienced persons at a higher frequency than opioid naïve persons. One may speculate that in some cases the adverse events reported represent idiosyncratic reactions to a change in opioid formulation.

Table 4: adverse event tabulation from study FEN-USA-86 (table 18 from the study report)

	Duragesic Patch(es) 12.5 mcg/h				
HO Body Class/ HO-Preferred Term	**Total (N=227)**	**Age <65 Years (N=183)**	**Age ≥65 Years (N=44)**	**Opioid Naive (N=100)**	**Opioid Exposed (N=127)**
Subjects with Adverse Events	170 (74.9%)	139 (76.0%)	31 (70.5%)	78 (78.0%)	92 (72.4%)
Application Site Disorders	24 (10.6%)	21 (11.5%)	3 (6.8%)	15 (15.0%)	9 (7.1%)
Application Site Reaction	23 (10.1%)	20 (10.9%)	3 (6.8%)	14 (14.0%)	9 (7.1%)
Body as a Whole-General	54 (23.8%)	43 (23.5%)	11 (25.0%)	25 (25.0%)	29 (22.8%)
Fatigue[1]	23 (10.1%)	17 (9.3%)	6 (13.6%)	10 (10.0%)	13 (10.2%)
Influenza-Like Symptoms	9 (4.0%)	8 (4.4%)	1 (2.3%)	7 (7.0%)	2 (1.6%)
Oedema Peripheral	12 (5.3%)	11 (6.0%)	1 (2.3%)	4 (4.0%)	8 (6.3%)
Central and Peripheral Nervous System	75 (33.0%)	61 (33.3%)	14 (31.8%)	38 (38.0%)	37 (29.1%)
Dizziness	26 (11.5%)	15 (8.2%)	11 (25.0%)	12 (12.0%)	14 (11.0%)
Headache	42 (18.5%)	38 (20.8%)	4 (9.1%)	22 (22.0%)	20 (15.7%)
Gastro-Intestinal Class	83 (36.6%)	70 (38.3%)	13 (29.5%)	44 (44.0%)	39 (30.7%)
Constipation[1]	19 (8.4%)	15 (8.2%)	4 (9.1%)	13 (13.0%)	6 (4.7%)
Diarrhoea	10 (4.4%)	7 (3.8%)	3 (6.8%)	2 (2.0%)	8 (6.3%)
Dyspepsia	8 (3.5%)	6 (3.3%)	2 (4.5%)	6 (6.0%)	2 (1.6%)
Nausea[1]	56 (24.7%)	49 (26.8%)	7 (15.9%)	33 (33.0%)	23 (18.1%)
Vomiting[1]	13 (5.7%)	9 (4.9%)	4 (9.1%)	8 (8.0%)	5 (3.9%)
Psychiatric Disorders	43 (18.9%)	34 (18.6%)	9 (20.5%)	26 (26.0%)	17 (13.4%)
Somnolence[1]	25 (11.0%)	17 (9.3%)	8 (18.2%)	15 (15.0%)	10 (7.9%)
Respiratory System	35 (15.4%)	28 (15.3%)	7 (15.9%)	19 (19.0%)	16 (12.6%)
Pharyngitis	8 (3.5%)	7 (3.8%)	1 (2.3%)	5 (5.0%)	3 (2.4%)
Upper Respiratory Tract Infection	11 (4.8%)	10 (5.5%)	1 (2.3%)	6 (6.0%)	5 (3.9%)
Skin and Appendages	52 (22.9%)	45 (24.6%)	7 (15.9%)	30 (30.0%)	22 (17.3%)
Pruritus[1]	31 (13.7%)	29 (15.8%)	2 (4.5%)	20 (20.0%)	11 (8.7%)
Rash	9 (4.0%)	8 (4.4%)	1 (2.3%)	5 (5.0%)	4 (3.1%)
Sweating Increased	12 (5.3%)	8 (4.4%)	4 (9.1%)	5 (5.0%)	7 (5.5%)

[1]Defined as common opioid related adverse events
Note: Percentages are based on the total number of subjects per subgroup
Note: A subject who experienced more than one adverse event within a body class/preferred term is counted once within that body class/preferred term.

7.1.5.4 Common adverse event tables

The common adverse events presented in the table below are those that occurred with a frequency of 1% or more during the clinical study, FEN-USA-86, which enrolled opioid-naïve and opioid-exposed patients. The data from the studies done in healthy volunteers has been presented above in section 7.1.5.3. I have not incorporated the adverse events from those studies in the table below since those studies used naltrexone which may have confounded the results.

The patients in study FEN-USA-86 were taking Duragesic doses that ranged from 12.5 to37.5 mcg/hr. Some o f the participating patients had been opioid naïve prior to study enrollment. The common adverse events presented in table 5 are similar to those included in the current approved labeling for this product. Adverse events noted during the trial which are not already incorporated into the label are denoted in **bold** font.

Table 5: Common adverse events occurring at 1% or more during study FEN-USA-86

Body System	Adults (n=227)
Body as a Whole	**Fatigue, back pain, fever, influenza-like symptoms, accidental injury,** peripheral edema, **rigors**
Gastrointestinal disorders	Nausea, abdominal pain, vomiting, constipation, dry mouth, diarrhea, dyspepsia
Musculoskeletal disorders	Arthralgia
Nervous/psychiatric	Somnolence, hypesthesia, anxiety, impaired concentration, dizziness, **insomnia,** nervousness, headache, ataxia
Respiratory	Dyspnea, hypoventilation, , pharyngitis, hiccups, **bronchitis, rhinitis, sinusitis, upper respiratory tract infection**
Skin and Appendages	Diaphoresis, pruritus, rash, application site reactions
Urogenital	**Micturition disorder**
Special Senses	Vision abnormal

The fever, bronchitis, rhinitis, sinusitis, upper respiratory tract infection and influenza-like symptoms, in my opinion, reflect the time when the study was performed which was during the cold and flu season from August through February. I do not feel that they represent drug-induced bronchospasm.

7.1.5.5 Identifying common and drug-related adverse events

The submitted studies were open-label, however, it is reasonable to assume that the Duragesic 12 mcg/hr system would have the same opioid-related adverse events that are seen with the currently approved higher strengths of Duragesic.

Duragesic is applied to the skin for administration of fentanyl. Rash, erythema and application site pruritis are commonly reported product-related adverse events.

7.1.5.6 Additional analyses and explorations

No additional analyses or explorations were performed in the review of this submission.

7.1.6 Less Common Adverse Events

No less common adverse events that are not currently known to be associated with Duragesic were found during the review of this submission.

7.1.7 Laboratory Findings

7.1.7.1 Overview of laboratory testing in the development program

Study FEN-USA-86 did laboratory testing (chemistry, hematology and urinalysis) both during screening and at study termination. Five patients with altered liver function tests on day 28 were noted: increased SGPT, increased GGT, and increased LDH were reported. In no instance were the altered values at the twice the upper limit of normal, all were minor elevations without clinical significance.

The central laboratory noted that four patients had laboratory values on day 28 that warranted notification of the study investigators: one case of elevated uric acid, one case of low RBC, and two cases of high RBCs. The study investigators did not feel that these abnormalities warranted removal from the trial nor did they consider the findings clinically serious. Based on the data presented, I concur with that assessment.

7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

This section is not applicable for this efficacy supplement.

7.1.7.3 Standard analyses and explorations of laboratory data

This section is not applicable for this efficacy supplement.

7.1.7.4 Additional analyses and explorations

This section is not applicable for this efficacy supplement.

7.1.7.5 Special assessments

This section is not applicable for this efficacy supplement.

7.1.8 Vital Signs

7.1.8.1 Overview of vital signs testing in the development program

In study FEN-USA-86, vital signs were measured on Study days 1, 2, 7, 16 and 28.

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

This section is not applicable for this efficacy supplement.

7.1.8.3 Standard analyses and explorations of vital signs data

There were no significant changes from baseline in viral signs over the 28 day study period, as may be seen from the table below.

Table 6: mean change from baseline (table 23 from the study report)

Parameter	Duragesic Patch(es) 12.5 mcg/h	
	Baseline Mean (SE) (N=227)	Mean Change (SE) (N=193)
Pulse, beats/minute	77.4 (0.65)	-0.5 (0.68)
Systolic BP, mmHg[a]	124.7 (1.13)	-0.4 (1.05)
Diastolic BP, mmHg[a]	77.5 (0.64)	-1.6 (0.68)
Respiration, breaths/minute	16.9 (0.14)	-0.2 (0.18)
Temperature, Fahrenheit	97.87 (0.06)	0.04 (0.06)

[a] Measured with subject seated.

7.1.8.4 Additional analyses and explorations

No additional analyses or explorations were done for this efficacy supplement.

7.1.9 Electrocardiograms (ECGs)

Electrocardiograms were performed during screening to verify eligibility. No follow-up electrocardiograms were done at trial termination.

7.1.9.1 Overview of ECG testing in the development program, including brief review of preclinical results

This section is not applicable for this efficacy supplement.

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

This section is not applicable for this efficacy supplement.

7.1.9.3 Standard analyses and explorations of ECG data

This section is not applicable for this efficacy supplement.

7.1.9.4 Additional analyses and explorations

This section is not applicable for this efficacy supplement.

7.1.10 Immunogenicity

This section is not applicable for this efficacy supplement.

7.1.11 Human Carcinogenicity

No human carcinogenicity studies were done for this efficacy supplement.

7.1.12 Special Safety Studies

No special safety studies were done for this efficacy supplement.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

The phenomena of opioid withdrawal is well known with documented signs and symptoms. The clinical signs associated with opiate withdrawal include lacrimation, yawning, diaphoresis, tremor, emesis, and rhinorrhea. The clinical symptoms associated with opiate withdrawal include sensations of being hot or cold, arthralgia, myalgia, abdominal cramping and formication. Withdrawal symptoms may occur, with or without a concurrent increase in pain symptoms, during conversion from/to oral opioids to Duragesic.

Opiates are known to have abuse potential. The proposed 12 mcg Duragesic system does not have an abuse potential that differs from the currently marketed transdermal fentanyl products. Patients who use opioids on a chronic basis may be expected to develop tolerance as well as physical dependence.

The Duragesic 12 mcg/hr system would be scheduled as a CII controlled substance as are the other strengths of Duragesic.

7.1.14 Human Reproduction and Pregnancy Data

The current Duragesic labeling notes that fentanyl is associated with impaired fertility and embryocidal effects in rats when given at intravenous doses 0.3 times the human dose for 12

days. There is no evidence of teratogenic effects in rodents. Duragesic is currently considered pregnancy category C. There is no data from adequate and well-controlled studies on the use of Duragesic in pregnant women.

Fentanyl is known to be excreted in human breast milk, therefore it is not recommended for use in nursing women.

7.1.15 Assessment of Effect on Growth

No assessment of effect on growth was done for this efficacy supplement.

7.1.16 Overdose Experience

The most significant risk of fentanyl use is that of respiratory depression. The appropriate response to overdose includes removal of the Duragesic system and patient stimulation with or without adjunctive use of an opioid antagonist. If necessary, artificial ventilation may be utilized. While opioid antagonists are commonly used clinically for acute treatment of overdose, it must be recognized that since transdermal fentanyl administration is associated with a skin depot effect the period of hypoventilation may be prolonged and opioid antagonist treatment may need to be extended. The contraindications section of the label warns that any patient who experiences an adverse event should be monitored after removal of the system since the serum concentration declines gradually due to the skin depot effect.

7.1.17 Postmarketing Experience

Hypoventilation leading to death has been reported in patients given Duragesic for the management of acute or post-operative pain. The boxed warning for this product lists postoperative use as a contraindication along with acute pain.

Postmarketing adverse event reports received by the agency along with periodic safety updates provided by ALZA reveal that reproductive system disorders such as decreased libido, decreased testosterone levels, erectile dysfunction, ejaculatory difficulty and anorgasmia are not uncommonly reported in association with chronic Duragesic use. The frequency of these types of disorders amongst the chronic pain population using scheduled opioids is not known so it not possible to say whether the frequency of these disorders among persons using Duragesic is higher or lower than the frequency of these disorders in persons using other types of opioids.

7.2 Adequacy of Patient Exposure and Safety Assessments

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

7.2.1.1 Study type and design/patient enumeration

Table 7: study design and patient enrollment/completion

	Study type	Number of subjects	Study duration
FEN-USA-86	Open-label safety	227 enrolled, 194 completed	28 days
FEN-BEL-9	Pharmacokinetics	8 enrolled, 8 completed	5 days
FEN-GBR-19	Bioequivalence	33 enrolled, 32 completed	72 hours

The sponsor did two new biopharmaceutics trials with the 12 mcg/hr patch in support of this application: FEN-GBR-19: A bioequivalence study which compared 4 Duragesic 12-mcg systems to 2 Duragesic 25 mcg systems, FEN-BEL-9: A clinical pharmacology study designed to evaluate the pharmacokinetics after a single application of a 12 mcg Duragesic system. The sponsor performed one uncontrolled safety and clinical utility study in 227 adults with chronic pain: FEN-USA-86.

7.2.1.2 Demographics

Table 8:Study participant demographics

	Statistics	USA-86	BEL-9	GBR-19
Number (n)		227	8	33
Age in years	Mean Range	52 years 19-88 years	36 years 23-44 years	29 years 20-45 years
Sex (n)	Male Female	35 % (80) 65 % (147)	50% (4) 50% (4)	64 % (20) 36 % (12)
Race (n)	White Hispanic Black Asian Other	89 % (203) 5 % (12) 5 % (12) 0 % 0 %	100% 0 % 0 % 0 % 0 %	97 % (32) 0 % 0 % 0 % 3 % (1)

7.2.1.3 Extent of exposure (dose/duration)

Table 9: Extent of exposure (dose/duration)

	0-3 days	4-7 days	8-14 days	15-21 days	22-28 days
# of patients	39	16	8	8	197

The table above shows the number of people who had an exposure duration corresponding to the range given. The 16 people in the third and fourth groups represent those patients on study FEN-USA-86 who dropped out during the given time periods.

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

7.2.2.1 Other studies

No other studies were reviewed during the evaluation of this efficacy supplement. Although study FEN-USA-86 was originally submitted to the IND and not the NDA, it was provided by ALZA for review in this efficacy supplement.

7.2.2.2 Postmarketing experience

This reviewer has reviewed the data submitted in the weekly summary of AERS data since August 2002 as well as the periodic safety reports (PSUR) provided by ALZA.

7.2.2.3 Literature

No independent literature review was performed during the review of this efficacy supplement.

7.2.3 Adequacy of Overall Clinical Experience

Duragesic has been marketed since 1990 so the agency has extensive knowledge of this product, albeit in higher dosage strengths. All tests reasonably applicable were conducted to assess the safety of this product, which represents a lower dosage strength than the currently approved and marketed Duragesic dosages: 25 mcg/hr, 50 mcg/hr, 75 mcg/hr and 100 mcg/hr.

The open-label design used for the three studies was adequate to provide biopharmaceutical information as well as additional safety information.

In addition to the safety information on the 227 patients exposed to Duragesic 12 mcg/hr systems, the Agency has extensive information on this product in the marketed dosages in the chronic pain population.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

This section is not applicable for this efficacy supplement.

7.2.5 Adequacy of Routine Clinical Testing

The routine clinical testing, including monitoring of laboratory parameters, vital signs, ECG and adverse events, was adequate.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

This section is not applicable for this efficacy supplement. The agency has data on fentanyl drug-drug interactions which has already been incorporated into the labeling for this product.

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

This section is not applicable for this efficacy supplement as this is not a new drug moiety.

7.2.8 Assessment of Quality and Completeness of Data

The data provided was of good quality and was complete.

7.2.9 Additional Submissions, Including Safety Update

The one clinical study and two pharmacokinetics studies were completed well before the NDA submission , no additional clinical submissions were received for this submission. We receive post marketing data and information on clinical trials being performed with Duragesic in the marketed strengths through other means.

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

The most clinically relevant drug-related events are somnolence, headache, nausea and vomiting. These are all known opioid-related adverse events and have been fully described in the opioid literature.

The most clinically relevant product-related event is application-site reaction, which may range from erythema to local pruritis. This is a known Duragesic related adverse event and has been fully described in the literature and elsewhere, e.g. the review for submission number 036 to this NDA.

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

7.4.1.1 Pooled data vs. individual study data

This section is not applicable for this efficacy supplement as the data was not pooled. Two of the studies were done in naltrexone blocked volunteers. The use of naltrexone may have been a confounding variable. Only one clinical study was provided for review.

7.4.1.2 Combining data

This section is not applicable for this efficacy supplement.

7.4.2 Explorations for Predictive Factors

This section is not applicable for this efficacy supplement.

7.4.2.1 Explorations for dose dependency for adverse findings

This section is not applicable for this efficacy supplement.

7.4.2.2 Explorations for time dependency for adverse findings

This section is not applicable for this efficacy supplement.

7.4.2.3 Explorations for drug-demographic interactions

This section is not applicable for this efficacy supplement.

7.4.2.4 Explorations for drug-disease interactions

This section is not applicable for this efficacy supplement.

7.4.2.5 Explorations for drug-drug interactions

This section is not applicable for this efficacy supplement.

7.4.3 Causality Determination

The most clinically relevant drug-related events are somnolence, headache, nausea and vomiting. These are all known opioid-related adverse events and have been fully described in the opioid literature.

The most clinically relevant product-related event is application-site reaction, which may range from erythema to local pruritis. This is a known Duragesic related adverse event.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

This product, Duragesic 12mcg/hr, is designed for use in dose titration between the currently marketed dosages of Duragesic: 25 mcg/h, 50 mcg/h, 75 mcg/h, 100 mcg/h.

8.2 Drug-Drug Interactions

[Reviewer's note: The following information comes verbatim from the approved labeling for Duragesic.]

> "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 significantly reduced.
>
> Since the metabolism of fentanyl is mediated by the CYP3A4 isoenzyme, coadministration of drugs that inhibit CYP3A4 activity may cause decreased clearance of fentanyl. The expected clinical results would be increased or prolonged opioid effects. Cytochrome P450 inducers, induce metabolism and as such may cause increased clearance of fentanyl.
>
> Fentanyl may be expected to have additive effects when used in conjunction with alcohol, other opioids, or illicit drugs that cause central nervous system depression."

8.3 Special Populations

The sponsor did not perform safety studies in special populations for this submission.

8.4 Pediatrics

Duragesic in the currently marketed 25, 50, 75, and 100 mcg strengths has been approved for administration to opioid-tolerant children aged 2 years and older. In supplement 036, dated November 25 2002, ALZA submitted pediatric studies for review in response to a pediatric written request. The interested reader is referred to that NDA review for details of the studies performed. The studies were summarized as follows (the following paragraphs were taken from the NDA19-813, sN036 review):

"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.

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.

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

8.5 Advisory Committee Meeting

The Division did not convene a meeting of the advisory committee in association with this efficacy supplement.

8.6 Literature Review

A literature review was not performed in association with this efficacy supplement.

8.7 Postmarketing Risk Management Plan

ALZA did not propose a risk management plan in this efficacy supplement.

8.8 Other Relevant Materials

No other relevant materials were reviewed in association with this efficacy supplement.

9 OVERALL ASSESSMENT

9.1 Conclusions

We were not provided with adequate information to confirm or deny efficacy of Duragesic 12 mcg/hr as a stand-alone dosage strength.

The safety information provided indicates that the most clinically relevant drug-related events are somnolence, headache, nausea and vomiting. These are all known opioid-related adverse events and have been fully described in the opioid literature. The most clinically relevant product-related event is application-site reaction, which may range from erythema to local pruritis. Opioid-naïve patients are noted to have had a higher incidence of some of the more common adverse events. Duragesic is not indicated for opioid naïve persons at any dosage.

9.2 Recommendation on Regulatory Action

I recommend approval of the Duragesic 12 mcg transdermal system as a titration step between the currently marketed Duragesic dosage strengths: 25 mcg/hr, 50 mcg/hr, 75 mcg/hr, 100 mcg/hr. The safety profile for this product does not differ from the approved fentanyl transdermal systems.

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

ALZA has expressed concern that fentanyl abuse may be a growing problem in the American market (citizen's petition dated 24 November 2004, Docket # # 2004P-0506). The Division of Anesthetic, Critical Care and Addiction drug products (DACCADP), shares this concern. In light of the material submitted by ALZA on the potential for abuse of the transdermal fentanyl system, as well as proprietary information on fentanyl abuse provided to us by the Agency's Controlled Substances Staff (CSS), we agree that a risk management plan (RMP) may be warranted to address concerns related to the abuse, misuse and diversion of gel-in-reservoir fentanyl transdermal systems such as Duragesic. We, along with CSS and the Office of Drug Safety (ODS), would support ALZA's efforts to devise such a plan.

9.3.2 Required Phase 4 Commitments

There are no required phase 4 commitments for this efficacy supplement.

37 Page(s) Withheld

_____ Trade Secret / Confidential

✓ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Medical- 1a

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-813 / S - 039

CHEMISTRY REVIEW(S)

NDA 19-813

Duragesic®
(Fentanyl Transdermal System)
12μg/hr Strength

Jila H. Boal, Ph. D.

Division of Anesthetics, Critical Care,
and Addiction Drug Products
(HFD-170)

Table of Contents

Table of Contents 2

Chemistry Review Data Sheet 3

The Executive Summary 7

I. Recommendations 7

A. Recommendation and Conclusion on Approvability 7

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable 7

II. Summary of Chemistry Assessments 7

A. Description of the Drug Product(s) and Drug Substance(s) 7

B. Description of How the Drug Product is Intended to be Used 8

C. Basis for Approvability or Not-Approval Recommendation 8

III. Administrative 9

A. Reviewer's Signature 9

B. Endorsement Block 9

C. CC Block 9

Chemistry Assessment 10

I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body Of Data 10

S DRUG SUBSTANCE [Name, Manufacturer] 10

P DRUG PRODUCT [Name, Dosage form] 14

A APPENDICES 63

R REGIONAL INFORMATION 64

II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1 64

A. Labeling & Package Insert 64

B. Environmental Assessment Or Claim Of Categorical Exclusion 66

III. List Of Deficiencies To Be Communicated 67

Chemistry Review Data Sheet

1. NDA #: 19-813

2. REVIEW #: 1

3. REVIEW DATE: July 21, 2004
   Revised January 20, 2005

4. REVIEWER: Jila H. Boal, Ph. D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
None	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original Supplement SE2-039	April 5, 2004
Amendment BL	November 24, 2004

7. NAME & ADDRESS OF APPLICANT:

Name:	Alza Corp.,
Address:	1900 Charlestown Rd., Mountain View, CA 94039- 7210.
Representative:	Ms. Elizabeth Clark, Senior Director, RA.
Telephone:	

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Duragesic□

b) Non-Proprietary Name (USAN): Fentanyl trandermal systems
c) Code Name/# (ONDC only): None
d) Chem. Type/Submission Priority (ONDC only):
   - Chem. Type:
   - Submission Priority:

9. LEGAL BASIS FOR SUBMISSION:
Supplement SCS-039 is for extension of the strength to a lower dose of 12µg/h patch.

10. PHARMACOL. CATEGORY: Analgesic

11. DOSAGE FORM: Transdermal patch

12. STRENGTH/POTENCY: 12 µg/h patch

13. ROUTE OF ADMINISTRATION: Transdermal

14. Rx/OTC DISPENSED: __X__Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
None.

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:
These are provided in the drug substance review section.

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	24, 417	Duragesic® Fentanyl Transdermal System

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	Not consulted because		

	it was not needed. 12 months real time stability data was submitted and 12 months expiration dating is granted.		
EES	Acceptable	October 12, 2004	Shirnette D Ferguson
Pharm/Tox	Consulted	January 05, 2005	Dan Mellon Ph.D.
Biopharm	Not consulted		
LNC	Not consulted		
Methods Validation	Not required		
OPDRA	Not consulted		
EA	Not required categorical exclusion was granted		
Microbiology	Not required		

61 Page(s) Withheld

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_____ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Chemistry- 1a

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

/s/

Jila Boal
1/21/05 05:10:16 PM
CHEMIST

Ravi Harapanhalli
1/21/05 05:39:17 PM
CHEMIST
AP recommendation with a caveat that the listed issues should be agreed to by the firm through a quick teleconference.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-813 / S - 039

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology and Biopharmaceutics Review

NDA:	**19-813**
Supplement:	**SE2-039**
Generic Name	Fentanyl Transdermal System
Brand Name:	**DURAGESIC 12.5 mcg/h Dosage Strength (Also referred to as 12 mcg/h)**
Formulations:	Transdermal Patch (12.5 mcg/h)
Route of Administration:	Topical
Indication:	Pain Relief
Type of Submission:	Supplemental NDA (New Patch Size/Strength)
Sponsor:	Alza, Mountain View, CA
Reviewer:	Sayed (Sam) Al Habet, R.Ph., Ph.D.
Team Leader	Suresh Doddapaneni, Ph.D.
Date of Submission:	April 5, 2004
Date Assigned:	December 3, 2004
Review Date:	December 25, 2004
First Draft:	January 4, 2005
Second Draft:	January 10, 2005
DFS Version:	January 14, 2005

TABLE OF CONTENTS

Page Contents/Study Description			Page #
Cover page			1
Table of Contents			2
1.0	Executive Summary		3-4
	1.1	Recommendation	3
	1.2	Phase 4 Commitments	3
	1.3	Summary of Important Clinical Pharmacology and Biopharmaceutics	3-4
	1.4	Signatures Page	5
2.0	Clinical Pharmacology and Biopahrmaceutics Review (Question Based review-QBR)		6-19
	2.1 General Attribute		6
	2.2 General Clinical Pharmacology		7-10
	2.3 Intrinsic Factors		10
	2.4 Extrinsic Factors		10
	2.5 Biopharmaceutics Issues		11-18
	2.6 Analytical Issues		20
3.	Detail Labeling Recommendation		21
4.	Appendices		21
	4.1	Proposed Package Insert	21-37
	4.2	Individual Study Review	38-43
	4.3	Consult Review (Pharmacometric)	43
	4.4	Filing Memo	44-45

1. Executive Summary:

1.1 Recommendation:

The office of Clinical Pharmacology and Biopharmacetuics finds the supplement SE2-039 to the NDA acceptable, provided that a satisfactory agreement can be reached between the Agency and sponsor regarding the language in the package insert.

1.2 Phase 4 Commitments

No Phase IV commitment is applicable for this supplement.

1.3 Summary of Clinical Pharmacology and Biopharmacetuics Findings

This is a supplemental NDA for a new strength/size of Duragesic (Fentanyl) transdermal patch of 12.5 mcg/h. To avoid confusion and prescribing errors with 125 mcg/h dose, the patch will be labeled as 12 mcg/h rather than 12.5 mcg/h. This patch will deliver a dose of 12.5 mcg fentanyl per hour. The active area of the patch is — half that of the 25 mcg/h Duragesic patch, and contains — of fentanyl.

The sponsor stated that the main rational for this new dosage strength is to allow for dose titration in certain patients with chronic pain. Duragesic is currently available in four strengths delivering 25, 50, 75, and 100 mcg fentanyl per hour. All Duragesic patches are designed to deliver a continuous fentanyl over 72 hours period for management of chronic pain. According to the labeling instruction, a new skin site should be used each time.

In this sNDA the sponsor submitted one bioequivalence study comparing the new strength patch with the currently marketed 25 mcg/h patch. Specifically, the study was designed to compare 4 x 12.5 mcg/h with 2 x 25 mcg/h Duragesic patches. In other words, the total dose in each arm of the study was 50 mcg/h. Fentanyl plasma concentration-time profiles were also very similar following both treatments (see later discussion). From this study, it can be concluded that the 12.5 mcg/h patch is bioequivalent to 25 mcg/h (**Figure 1.3.1 and Table 1.3.1**).

Figure 1.3.1 Mean Serum Fentanyl Plasma concentration-Time Profiles Following 4 x 12.5 mcg/h and 2 x 25 mcg/h Duragesic Patches

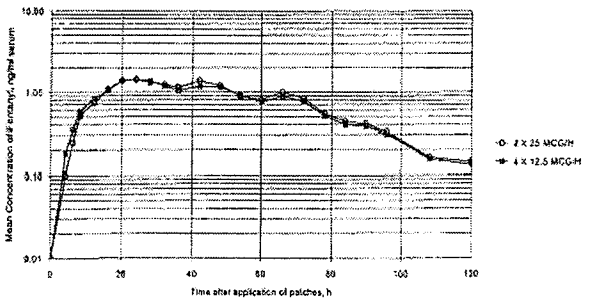


Table 1.3.1. Mean (± SD) PK Parameters Following 4 x 12.5 mcg/h and 2 x 25 mcg/h Duragesic Patches

	4 x 12.5 mcg/h Patches		2 x 25 mcg/h Patches		90% CI
Parameters	Mean	SD	Mean	SD	**(for log Parameters)**
AUC (0-inf) (ng.h/ml)	91.52	30.18	94.82	26.47	89-101
AUC (0-t) (ng.h/ml)	81.89	26.54	87.55	23.75	87-98
Cmax (ng/ml)	1.52	0.52	1.62	0.483	87-100
Tmax (h)	29.40	9.74	32.27	13.40	-
T ½ (h)	24.09	9.19	25.49	15.73	-

What are the Main Findings?

From the submitted studies, the following conclusions can be made:

- The fentanyl serum concentration-time profiles following the two treatments were similar (**Figure 1.3.1**).
- The lag time before fentanyl appearance in the plasma was approximately 8 hours following both treatments. In addition, the steady state was achieved within 24 hours of application of either patch.
- The 4 x 12.5 mcg/h patches were bioequivalent to 2 x 25 mcg/h patches based on the 90% CI limits for both Cmax and AUC as they were within the recommended regulatory limits of 80-125% (**Table 1.3.1**). The 90% CI limits were very tight for both Cmax and AUC as they range from 87-101.
- The Cmax following 4 x 12.5 mcg/h patches (i.e., 50 mcg/h dose) of Duragesic is proportional to 2 x 25 mcg/h patches (i.e., 50 mcg/h dose).
- From the summary data reviewed by OCPB within the BE study, no safety related issues were noted.
- According to the sponsor, Duragesic 12.5 mcg/h was found to provide adequate analgesia in pediatric population under a variety of clinical circumstances. These data were based on the uncontrolled clinical studies that were crossed referenced in this NDA. However, these studies were not reviewed by OCPB. Therefore, the final conclusion on these data will be made by the Medical Officer.
- In the reviewer's opinion, the historical safety data of the use of Duragesic at higher doses should negate any safety concern from the proposed lower dose of 12.5 mcg/h.

Reviewer

Sayed (Sam) Al Habet, R.Ph., Ph.D.
Office of Clinical Pharmacology and Biopharmaceutics
Division of Pharmaceutical Evaulation II

Final version signed by Suresh Doddapaneni, Ph.D., Team Leader----------

cc: HFD-570, HFD-870 (Al Habet, Doddapaneni, and Malinowski), Drug file (Biopharm File, Central Document Room).

2.0
Clinical Pharmacology and Biopharmaceutics Review (Question Based Review)

2.1 What are the General Attributes of Duragesic?

2.1.1 What is the Rationale of the New Duragesic Strength?

This new strength is mainly for titration of those patients that require fine tuning in their therapeutic dose. Fentayl is a narrow therapeutic index drug and any small changes in the dose, drug release, or plasma concentration may have therapeutic consequences. The new 12.5 mcg/h strength may allow an intermediate increase and/or decrease in dosage regimen between 12.5 mcg/h to 112.5 mcg/h or higher based on the currently marketed strengths of 25, 50, 75, and 100 mcg/h patches.

According to the sponsor, this new low dosage strength will allow for a smaller dose adjustment if required. Based on the dosing guidelines for Duragesic, a 25 mcg/h step increase is recommended (current Package insert). The reason for this is that the 25 mcg/h is the smallest commercially available patch strength. For some patients this step increase may be unnecessarily high as it represents 100% and 50% increase in dose in those patients who are already receiving 25mcg/h or 50 mcg/h patches, respectively, with corresponding increases in fentanyl blood levels. The availability of a lower dose, such as the 12.5 mcg/h patch, would allow for a more gradual titration step from 25 mcg/h to 50 mcg/h, two of the currently available doses, thereby reducing use of rescue medication.

Additionally, the sponsor stated that "this patch could be utilized in those patients whose treatment is initiated with a 25 mcg/h patch but who cannot tolerate this dose...." Therefore, this patch size "would provide a titration step down that may allow a patient to acclimatize to the treatment more easily, thereby permitting a titration back to the 25 mcg/h patch and beyond, as required." It should be emphasized again that OCPB did not review the efficacy data in this supplement. Therefore, the final conclusion on the efficacy of a single 12.5 mcg/h patch will be made by the Medical Officer.

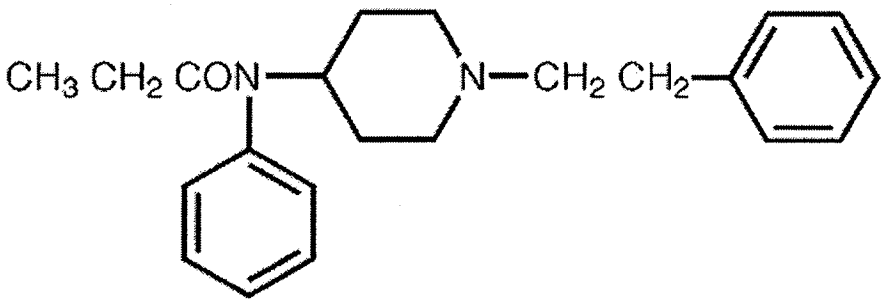
2.1.2 What is the Regulatory History of Fentanyl and Duragesic?

Duragesic was first approved in the United States in 1990 for 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.

2.2 What is the General Clinical Pharmacology?

What is Fentanyl as a Drug Substance?

- Fentanyl is a 40 year old drug that has been in clinical use as intravenous analgesic and anesthetic.
- The molecular weight of fentanyl base is 336.5 and its structural formula is as follows:



Structure of Fentanyl

- In the last decade fentanyl has been formulated as transdermal delivery system under the trade name Duragesic available in four strengths: 25, 50, 75, and 100 mcg/h. These patches provide 72 hours analgesia in in-patient and out-patients settings with chronic pain.
- 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 (**Table 2.2.1**).

Table 2.2.1. Content of the Currently Marketed and the Proposed Duragesic Patches

Dosage Strength (mcg/h)	Target Drug Content (mg)	Active area (cm^2)
12.5[a]	1.25	5
25	2.5	10
50	5.0	20
75	7.5	30
100	10.0	40.

[a] This dosage strength is referred to as 12 mcg/h in the labeling.

- As opioid analgesic it interacts with opioid µ-receptor which is predominantly distributed in the human brain, spinal cord, and other tissues. The analgesia and sedation produced by fentanyl is primarily through its effects on the central nervous system.
- Apart from its primary actions on the central nervous system such as analgesia, sedation, and euphoria, it acts on other systems leading to side effects such as respiratory depression, constriction of pupil, nausea and vomiting, and postural syncope.

2.2.1 What are the Relevant PK Characteristics of Fentanyl and Duragesic?

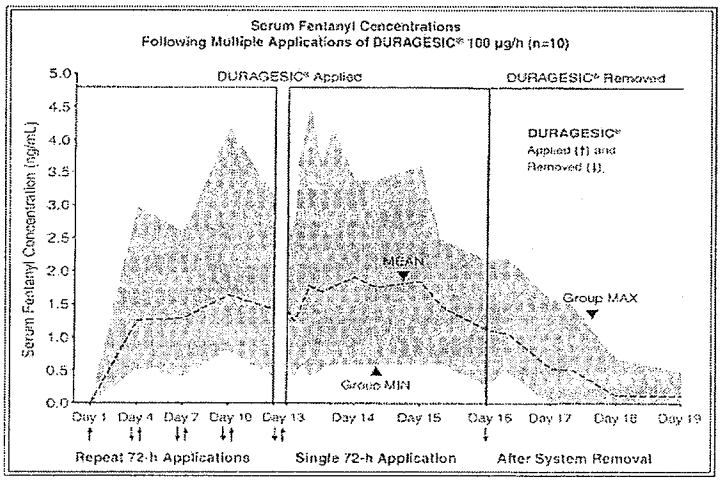
Release Characteristics:

- When formulated in a patch, fentanyl moves in the direction of the lower concentration at a rate determined by the copolymer release membrane and its diffusion through the skin layers.
- The rate of delivery to the skin varies over the 72-hour.
- There is a wide inter-patient variation in the rate of fentanyl delivered from the patches. This variation is due to variation in skin thickness and diffusion.

Blood Levels:

- Serum fentanyl concentrations increase gradually following initial application of the patch and then leveling off between 12 and 24 hours and remain relatively constant for the remainder of the 72-hour application period (**Figure 2.2.1.1**).
- Peak serum concentrations of fentanyl generally occur between 24 and 72 hours after initial application.
- Fentanyl is considered a narrow therapeutic index drug. The minimum effective serum concentration of fentanyl ranges from 0.2 to 1.2 ng/mL. Above a concentration of 2 ng/mL side effects starts to appear.
- In general, serum fentanyl concentrations are proportional to patch size (dose).
- With continuous use, fentanyl reaches a steady state serum concentration after several applications.
- After system removal, serum fentanyl concentrations decline gradually, falling about 50% in approximately 17 h (range from 13 to 22 hours).
- In small children of 5 years or younger, fentanyl levels could be as twice higher as adults.

Figure 2.2.1.1. Mean Serum Fentanyl Concentration-Time Profiles Following Multiple Applications of Duragesic 100 mcg/h (source current package insert, n=10)



Elimination:

- Following IV administration the half-life of fentanyl is approximately 7 hours (ranging from 3 to 12 hours).
- The half-life in elderly patients could be prolonged.

Distribution:

- Fentanyl accumulates in the skeletal muscle and fat and is released slowly into the blood.
- The average volume of distribution of fentanyl

Metabolism:

- Fentanyl is metabolized primarily by CYP-3A4 isoenzyme system and undergoes oxidative N-dealkylation to norfentanyl and other inactive metabolites.
- Following IV administration, fentanyl is excreted mainly in urine with approximately 75% as metabolites and 10% as unchanged.

2.2.2 What Studies are submitted in the Current NDA?

Table 2.2.2 lists the two main clinical pharmacology studies submitted in this supplement and other related studies..

Table 2.2.2. Synopsis of all Studies Conducted with 12.5 mcg/h Duragesic Patches

Study #	Design	Objectives	Remarks
FEN-GBR-19	Single dose: 4 x 12.5 mcg/h vs 2 x 25 mcg/h patches	Bioequivalence	Pivotal Study
FEN-BEL-9	Single dose 12.5 mcg/h patch	Serum profiles	Pilot study
FEN-USA-87	Titration study: 12.5, 25, 50, 75, and 100 mcg/h	Safety and clinical utility in pediatrics	Uncontrolled (S-036)
FEN-INT-24	12.5 mcg/h	Safety, clinical utility, and PK in 2-12 years old subjects	Uncontrolled (S-036)
FEN-USA-86	12.5 mcg/h titration up to 37.5 mcg/h x 28 days	Safety and clinical utility of titration in adults only	Uncontrolled (IND

A) PK Studies

The sponsor conducted one pivotal study to demonstrate the bioequivalence of **four** 12.5 mcg/h Duragesic patches with **two** 25 mcg/h Duragesic patches, the currently approved and marketed formulation (Study # FEN-GBR-19). Therefore, the approval of this new strength will be based mainly on this study. However, FEN-BEL-9 was a pilot study to establish fentanyl plasma-concentration time profiles following application of 12.5 mcg/h patches.

B) Clinical Studies:

No adequate and well-controlled studies have been conducted with Duragesic 12.5 mcg/h.

C) Cross Referenced Supportive Clinical Studies:

The sponsor crossed referenced three **uncontrolled** studies that were previously submitted under separate covers to evaluate the safety and clinical utility of Duragesic 12.5 mcg/h in adults and children.

Two of these studies were submitted under supplement # S-036. These two studies were conducted in pediatric subjects with chronic pain and the supplement was approved in May 20, 2003 (Studies # FEN-INT-24 and FEN-USA-87). The third study was submitted under IND # 24,417 serial # 104 in March 5, 2004. This study was conducted only in adult patients with chronic pain (Study # FEN-USA-86).

2.2.3 Does this Drug Prolong the QT or QTc Interval?

No specific QT study was conducted in this NDA. No QT prolongation signals was noted in the submitted studies.

It should be noted however that fentanyl may cause bradycardia and therefore it is contraindicated in patients with bradycardia.

2.3 Are there any Intrinsic Factors Affecting Dosage Regimen?

The development of tolerance and addiction to opioid play major rules in the management of chronic pain, dosage selection, titration process, and response. In addition, it is well known that there is marked inter-patient variation in response to opioid, and in particular in the management of chronic pain. These factors would be considered during the titration process.

2.4 Are there any Extrinsic Factors Affecting Dosage regimen?

One factor that may be considered to affect the release of fentanyl from the patches is the variability in skin penetration between patients. However, once a particular patient has been titrated, little variation may be expected in fentanyl release, except the response may vary as tolerance is being developed.

2.5 Biopharmaceutics Issues

2.5.1 What is the Drug Product/Formulation?

This is a new patch strength containing the same composition of the currently marketed patches, except the size (**Tables 2.5.1.1 and 2.5.1.2**). The manufacturing technology is also the same as the currently marketed patches. **Figure** 2.5.1 shows the simplified schematics of 12.5 mcg/h patch. The formulations used in the clinical pharmacology studies and other studies are listed in **Table 2.5.1.3.**

Table 2.5.1.1. Content of the Currently Marketed and the Proposed Duragesic Patches

Dosage Strength (mcg/h)	Target Drug Content (mg)	Active area (cm^2)
12.5[a]	1.25	5
25	2.5	10
50	5.0	20
75	7.5	30
100	10.0	40

[a] This dosage strength is referred to as 12 mcg/h in the labeling.

Table 2.5.1.2. Quantitative Composition of Duragesic Patch

Duragesic® (fentanyl transdermal system) 12 mcg/h; Active System Area 5 cm^2				
	Component	Function	Quality Standard	Quantity
C				
T				

[a] Materials are identical to those currently used in the manufacture of the approved product.
[b] Weights shown are examples. Material is added to batch as a film.
[c] Solvent removed during processing.
[d] Material received as an incoming raw material.

Figure 2.5.1.1 (A and B). Simplified schematic of Duragesic 12.5 mcg/h Patch

Schematic A

Figure 2.5.1.1 (Schematic B)

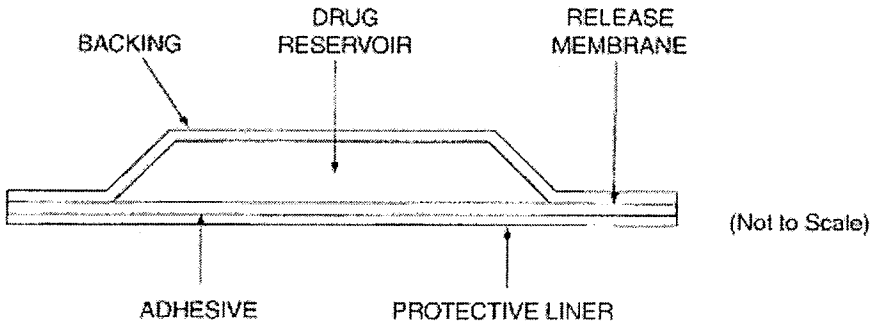


Table 2.5.1.3. Formulations Used in Clinical Pharmacology and Other Studies Studies

Item/Code ID/Control	Appendix	Stability Study No.	Clinical Study Protocol No.	Clinical Study Type[a]	Date Drug Added/ Site of Manufacture/ Date of End Manufacture	Batch Size (Number of Systems)	Drug Substance Item/Code ID/Control
0007897 9801242	Appendix A	2257	FEN-GBR-19 FEN-INT-24[d] FEN-BEL-9 FEN-USA-86[c] FEN-USA-87[c]	BE SCE/PK PK SCE/PK SCE/PK			
0007897 9807838[b]	Appendix B	2551	NA	NA			
0007897 9807879[b]	Appendix C	2552	NA	NA			
0007897 9807880[b]	Appendix D	2553	FEN-INT-24[d] FEN-USA-87[c]	SCE/PK SCE/PK			
0007897 0017475	Appendix E	3145	FEN-USA-87[c]	SCE/PK			
0007897 0209507	Appendix F	3642	FEN-USA-87[c]	SCE/PK			

NOTES: BE = Bioequivalence; NA = not applicable; PK = Pharmacokinetic; SCE = Safety
[a] See abbreviations at end of table for definition of clinical study type.
[b] Primary stability lot
[c] Clinical study is referenced but not included in this submission

2.5.1.1 What is the Relative Bioavailability of the Proposed to-be-marketed 12.5 mcg/h Formulation Following a Single Dose Administration Compared to the 25 mcg/h Reference Product?

Study # FEN-GBR-19 (Single Dose BE):

Objectives:

To evaluate the bioequivalence of Duragesic 12.5 mcg/h patch (Treatment A: 4 x 12.5 mcg/h patches) and the commercially available Duragesic 25 mcg/h patch (Treatment B: 2 x 25 mcg/h patches)

Design:

- This was a randomized, open-label, 2-way crossover study as follows:

Treatment A (test): 4 x 12.5 mcg/h patch (total dose = 50 mcg/h)

Treatment B (reference): 2 x 25 mcg/h patch (total dose = 50 mcg/h)

- The study was conducted in 33 healthy adults' subjects.
- All subjects received each treatment in crossover fashion, with a minimum of 6-day washout between the two treatment periods.
- Each patch was applied for 72 hours, consistent with the prescribing information for Duragesic.
- During the study, subjects received oral naltrexone 50 mg as an opioid antagonist, from the evening before study medication application and every 12 hours up to 48 hours after each patch removal.
- A total of 30 subjects completed the study

Results:

- Fentanyl serum concentration-time profiles following 4 x 12.5 mcg/h and 2 x 25 mcg/h patches were similar which include lag times, peak concentration, AUC, time to achieve steady state, and steady state levels (**Figure 2.5.1.1.1**).
- The mean geometric mean ratios (Treatments A/B) for AUCinf, AUClast, and Cmax ranged from 92% to 94%, and all 90% CIs were within the bioequivalence limits of 80% to 125% (**Table 2.5.1.1.1**).
- These results demonstrate bioequivalence of 12.5 mcg/h patches to 25 mcg/h patches.
- In addition, The Cmax of Duragesic 12.5 mcg/h strength is dose proportional to the 25 mcg/h strength. Based on the historical data, the Cmax increases from 0.3 to 2.5 ng/ml as the dose increases from 12.5 to 100 mcg/h (**Table 2.5.1.1.2 and Figure 2.5.1.1.2**). However, no information on the dose proportionality is available for AUC as study designs are different across studies to allow accurate and/or consistent estimate of AUCs.

Figure 2.5.1.1.1. Mean Serum Fentanyl Plasma concentration-Time Profiles Following 4 x 12.5 mcg/h and 2 x 25 mcg/h Duragesic Patches

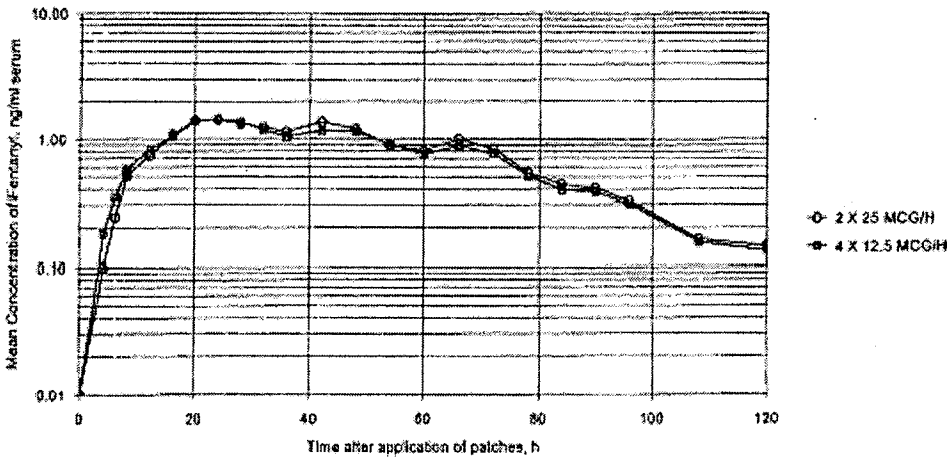


Table 2.5.1.1.1. Mean (± SD) PK Parameters Following 4 x 12.5 mcg/h and 2 x 25 mcg/h Duragesic Patches

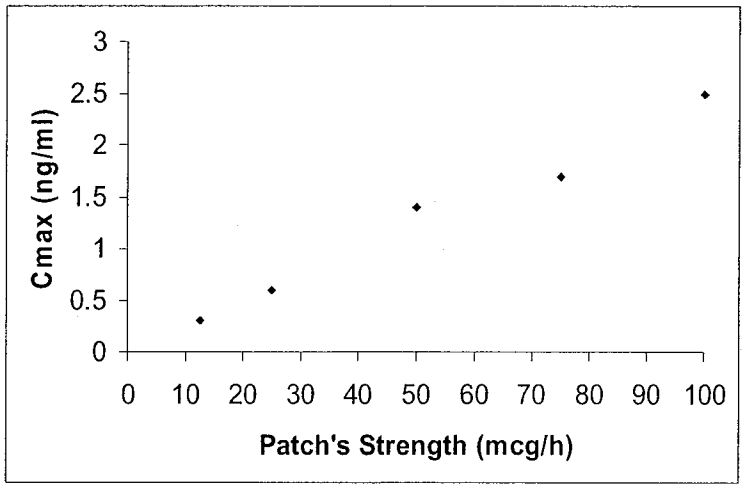
	4 x 12.5 mcg/h Patches		2 x 25 mcg/h Patches		90% CI
Parameters	Mean	SD	Mean	SD	**(for log Parameters)**
AUC (0-inf) (ng.h/ml)	91.52	30.18	94.82	26.47	89-101
AUC (0-t) (ng.h/ml)	81.89	26.54	87.55	23.75	87-98
Cmax (ng/ml)	1.52	0.52	1.62	0.483	87-100
Tmax (h)	29.40	9.74	32.27	13.40	-
T ½ (h)	24.09	9.19	25.49	15.73	-

Table 2.5.1.1.2. Historical PK Data to Demonstrate Dose Proportionality in Cmax

Dose	Mean (SD) t_{max}, h	Mean (SD) C_{max}, ng/ml
Duragesic 12 (12 mcg/h) [a]	27.5 (9.6)	0.3 (0.2)
Duragesic 25 (25 mcg/h) [b]	38.1 (18.0)	0.6 (0.3)
Duragesic 50 (50 mcg/h) [b]	34.8 (15.4)	1.4 (0.5)
Duragesic 75 (75 mcg/h) [b]	33.5 (14.5)	1.7 (0.7)
Duragesic 100 (100 mcg/h) [b]	36.8 (15.7)	2.5 (1.2)

[a] From FEN-BEL-9 clinical study (N=8).
[b] Duragesic (US) Package Insert (May 2003).

Figure2.5.1.1.2. Historical Data for Duragesic Patch's Strength and Cmax (Data Extracted for Table 2.5.1.1.2)



Conclusions:

- The 90% CI for both Cmax and AUC of fentanyl were within the bioequivalence (BE) limits of 80%-125%. Therefore, the new 12.5 mcg/h patch is bioequivalent to 25 mcg/h patch.
- No safety related issues were noted in this study.

2.5.1.2 Are There any Additional Supportive Clinical Pharmacology Studies?

Study FEN-BEL-9:

- This is a pilot study with the objective to determine the fentanyl serum concentration-time profile after one-time application of a single patch of 12.5 mcg/h for 72 hours duration. The study was conducted in 8 healthy adult subjects (4 males and 4 females). All subjects were Caucasians with a mean age of 36 (range from 23 to 44 years).
- Oral naltrexone 50 mg was given in the evening before study medication and every 12 hours up to 12 hours after patch removal.
- Blood was collected over 108 hours as shown in **Tables 2.5.1.2.1 and 2.5.1.2.2.** It should be noted that unlike in study FEN-GBR-19, fentanyl concentration was determined in plasma rather than serum.
- The batch number of 12.5 mcg/h patch used in this study is 9801242/A.
- Usual safety parameters were monitored in this study, including ECG.

Table 2.5.1.2.1 Study Flow chart

Study time (hours)	Medical history, lab tests, physical exam, and inf. consent	Naltrexone	Duragesic® applied/ removed (A/R)	ECG, HR, BP	Respiratory rate[2]	Blood sampling
screening	X			X		
-12		X				
0		X	A	X[1]	X	X
4					X	X
6					X	X
8					X	X
12		X		X[1]	X	X
16					X	X
20					X	X
24		X		X[1]	X	X
28					X	X
32					X	X
36		X			X	X
42					X	X
48		X		X[1]	X	X
54					X	X
60		X			X	X
66					X	X
72		X	R	X[1]	X	X
78					X	X
84		X			X	X
90					X	X
96				X[1]	X	X
108					X	X

[1] Additional measurements were performed every 2 hours while subjects were asleep.
[2] Only heart rate and blood pressure were recorded.

Table 2.5.1.2.2. Blood Sampling

Study Study Design	Study Subjects No. Subjects Evaluated	Study Medication(s)	Timing of Blood Samples for PK
Human Pharmacokinetic Study: FEN-BEL-9			
Open-label, 1-arm	Healthy non-smoking men or women (18–55 years) N=8	1 × Duragesic 12.5 mcg/h patch	Predose (0 h) and 4, 6, 8, 12, 16, 20, 24, 28, 32, 36, 42, 48, 54, 60, 66, 72, 78, 84, 90, 96, and 108 h after application.

Results:

- The plasma concentration-time profiles could be completely characterized during the entire time course of application and beyond after patch removal.
- After patch application, fentanyl serum concentrations gradually increased during the first day (**Figure 2.5.1.2.1**).
- The Tmax occurs at approximately 27 hours and the terminal half-life is approximately 20 hours (**Table 2.5.1.2.3**).

Figure 2.5.1.2.1 . Mean Fentanyl Plasma-Concentration Time Profile (Study FEN-BEL-9)

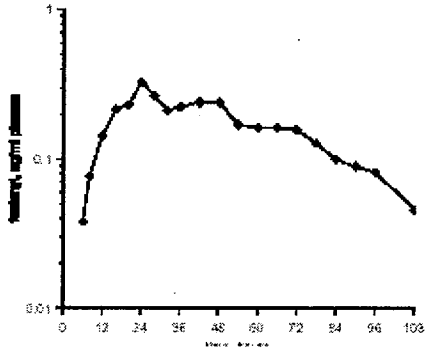


Table 2.5.1.2.3. Summary of PK Parameters (Study FEN-BEL-9)

Parameter/ CRFID	30007	30011	30006	30013	30003	30012	30002	30009	n	Mean ± SD	Median	Min	Max
t_{max}, h	24.0	24.0	16.0	24.0	20.0	42.0	42.0	28.0	8	27.5 ± 9.6	24.0	16.0	42.0
C_{max}, ng/ml	0.395	0.317	0.421	0.848	0.155	0.148	0.214	0.280	8	0.347 ± 0.226	0.299	0.148	0.848
AUC_{last}, ng.h/ml	17.5	15.7	18.9	30.0	9.90	9.70	15.1	17.2	8	16.8 ± 6.3	16.5	9.70	30.0
λ_z, 1/h	0.0416	0.0386	0.0461	0.0274	0.0429	0.0453	0.0217	0.0300	8	0.0367 ± 0.0091	0.0401	0.0217	0.0461
$t_{1/2term.}$, h	16.7	18.0	15.0	25.3	16.2	15.3	32.0	23.1	8	20.2 ± 6.1	17.4	15.0	32.0
AUC_{inf}, ng.h/ml	18.1	16.6	19.6	33.0	10.5	10.6	18.5	19.0	8	18.2 ± 7.0	18.3	10.5	33.0

2.5.3 What is the PK Characteristics of Fentanyl Following Multiple Dose Administration?

With continuous use, fentanyl reaches a steady state serum concentration after three to four applications.

2.5.4 What are the Proposed *In Vitro* Dissolution Methods and Specifications?

The sponsor used the approved *in vitro* dissolution method and specifications for 12.5 mcg/h patch as shown in **Table 2.5.4.1.** Briefly, the method consists of
media. Samples were collected at 2, 12, and 24 hours. The mean and individual data are shown in **Table 2.5.4.2** and the profile is shown in (**Figure 2.5.4.1**).

Conclusion:

From OCPB perspective, the provided *in vitro* dissolution data meets the approved specifications.

Table 2.5.4.1. *In vitro* Dissolution Method and Specifications for The Formulation lot Used in Clinical Pharmacology Studies

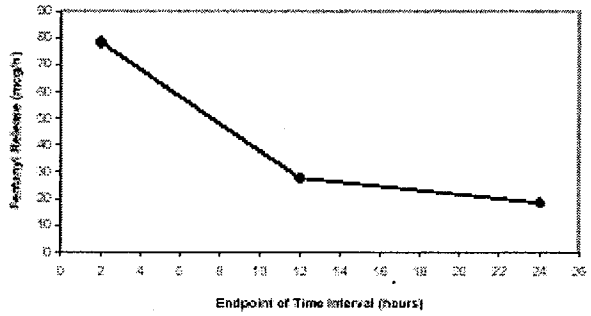
Date of Test:	
Dissolution of Apparatu	
Analytical Method:	
Media:	
Temperature:	
Collection Times:	6-12 hr, and 12-24 hr.
Units Tested	
Dose:	
Code No:	
Control No.	

Table 2.5.4.2. Sample Fentanyl Release (log clearance data) Data Used in Clinical Pharmacology Studies

Time (hrs)	Sample (mcg/h)													
	1	2	3	4	5	6	7	8	9	10	11	12	Avg[a]	%RSD

due to rounding

Figure 2.5.4.1. Sample Mean Fentanyl Release-Time Profile for 12.5 mcg/h Patches Used in Clinical Pharmacology Studies



2.6 Are There any Analytical Issues?

- The serum concentrations of fentanyl were determined by a validated radioimmunoassay (RIA) method that was originally developed in plasma. This was then subsequently validated for both plasma and serum (**Table 2.6.1**).
- This method was also used in the previously submitted pilot PK study (FEN-BEL-9).

Table 2.6.1. Summary of the Analytical Method Validation Parameters

[ ]

Results:

- [
-]
-

Conclusion:

- Based on the above information, the method is acceptable for the detemination of fentanyl concentration in serum.
- No analytical issues are noted in this NDA.

3. Detailed Labeling Recommendation

There are no major OCBP labeling comments on this NDA. All labeling comments will be made directly into the proposed label in conjunction with the other members of the review team.

25 Page(s) Withheld

_____ Trade Secret / Confidential

✓ 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/

Sayed Al-Habet
1/14/05 02:46:53 PM
BIOPHARMACEUTICS

Suresh Doddapaneni
1/18/05 07:31:26 AM
BIOPHARMACEUTICS

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-813 / S - 039

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY FOR NDA #19813 SUPPL #039

Trade Name DURAGESIC Generic Name Fentanyl transdermal system

Applicant Name ALZA Corporation HFD # 170

Approval Date If Known February 4, 2005

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy 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 a 505(b)(1), 505(b)(2) or efficacy supplement?
YES /X/ NO /___/ If yes, what type? 505(b)(1)/SE2

c) 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 /___/ **NO /X/**

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.

The sponsor's submitted study compared four 12 mcg/patches to two 25 mcg/h patches. The purpose of the study was only to demonstrate bioequivalence, not efficacy. The sponsor has termed this a bioequivalence study.

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:

d) Did the applicant request exclusivity? YES /___/ **NO /X/**

If the answer to (d) is "yes," how many years of exclusi-
did the applicant request?

e) Has pediatric exclusivity been granted for th'
Moiety? **YES /X/** NO /___/

If the answer to the above question i'
result of the studies submitted in re
Writen Request?

Pediatric exclusivity was granted with t

which was in response to a PWR. This supplement (S-039) is NOT in response to a PWR.

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?
YES /___/ **NO /X/**

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (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.

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 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.

YES /X/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 19-813 Duragesic (fentanyl transdermal system)
NDA# 20-747 Actiq (oral transmucosal fentanyl citrate)
NDA# 16-619 Sublimaze (fentany citrate injection)

2. Combination product.

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 ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.) 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 /___/ **NO /X/**

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

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.

(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 /___/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(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?

YES /___/ NO /___/

(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 /___/ 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 /___/ 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:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

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.")

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

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?

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) 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"):

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?

Investigation #1

IND # _____ YES /___/ NO /___/ Explain: _____

Investigation #2

IND # _____ YES /___/ NO /___/ Explain: _____

(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?

Investigation #1

YES /___/ Explain _____ NO /___/ Explain _____

Investigation #2

YES /___/ Explain _____ ! NO /___/ Explain _____

(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 /___/

If yes, explain: _____

Completed by:
Kimberly Compton 2-4-05
Regulatory Project Manager

Concurred by:
Bob Rappaport, M.D. 2-4-05
Division Director

Form OGD-011347 Revised 05/10/2004

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
2/4/05 04:22:04 PM

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA # : 19-813 **Supplement Type (e.g. SE5): SE2** **Supplement Number: 039**

Stamp Date: April 6, 2004 **Action Date: February 4, 2005**

HFD-170 **Trade and generic names/dosage form: Duragesic (fentanyl transdermal system)**

Applicant: ALZA Corporation **Therapeutic Class:**

Indication(s) previously approved:
DURAGESIC® is indicated for management of persistent, moderate to severe chronic pain

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 1

Indication #1:
The management of persistent, moderate to severe chronic pain that

Is there a full waiver for this indication (check one)?

- ☐ **Yes: Please proceed to Section A.**
- ■ **No: Please check all that apply: X Partial Waiver ____Deferred ____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: Studies have already been completed, submitted for review in patients 2 to 18 years of age (subject of S-036.)

Min: Newborn
Max: 2 years of age

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: <u>The pharmacokinetics and skin characteristics in children less than 2 years of age are different than in older children. Also, there is safety concern that metabolites could accumulate in children under 2 years of age. Additionally, conditions that warrant the use of this product in children less than 2 years of age are limited.</u>**

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._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ 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): _____

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._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Comments:

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}
<u>Kimberly Compton, R. Ph.</u>
Regulatory Project Manager

cc: **NDA 19-813/S-039**
HFD-960/ Grace Carmouze

For questions on completing this form contact the division of pediatric drug development, hfd-960, 301-594-7337.
(revised 12-22-03)

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/s/

Kimberly Compton
2/4/05 06:03:02 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

Form Approved: OMB No. 0910-0396
Expiration Date: February 28, 2006.

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

☐ (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators	
[redacted], MD (Study FEN-GBR-19) (*name changed to [redacted], MD since completion of study)	

☒ (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

☐ (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME	TITLE
Robert M. Clark	Vice President of Finance and CFO
FIRM / ORGANIZATION: ALZA Corporation	
SIGNATURE: [signature]	DATE: 3/19/04

Paperwork Reduction Act Statement

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Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

Created by: PSC Media Arts Branch (301) 443-1090 EF

Division of Anesthetic, Critical Care, and Addiction Drug Products

REGULATORY PROJECT MANAGER REVIEW

Application Number: NDA 19-813/S-039

Name of Drug: Duragesic (fentanyl transdermal patch)

Sponsor: Alza Corporation

Material Reviewed

Submission Date(s): April 5, 2004 (N 000) and November 24, 2004 (BL)

Receipt Date(s): April 6, 2004 and November 26, 2004 (BL)

Background and Summary Description: This submission proposes a new 12 mcg/hr dosage strength. The initial package insert (PI) labeling submitted did not address the updates requested by the Agency in the S-031 AE letter of May 20, 2003, which involved extensive changes to the PI. The Agency requested that the sponsor submit labeling updated to address these changes.

Updated labeling addressing the S-031 extensive changes was then the subject of the November 24, 2004 (BL) submission which is reviewed here. The PI submitted November 24, 2004 is compared to the PI submitted with S-036 (approved May 20, 2003, acknowledged and retained January 20, 2004).
The carton labels submitted November 24, 2004 are compared to the carton labels submitted with S-025 (submitted December 2, 1999, approved November 1, 2000) and the container labels submitted November 24, 2004, are compared to the container labels submitted with S-026 (submitted January 26, 2000, approved February 1, 2000.) The direct patch label ("printmat") was compared to the printmat submitted with S-020 (submitted July 8, 1996, approved July 17, 1997.)

Status Report

Reviews Completed: Kim Compton, RPM, January 15, 2005

Reviews Pending: ElizabethMcNeil, M.D., Medical Officer, Jila Boal, Ph.D., CMC Reviewer, Sayed Al-Habet, Ph.D., Biopharmaceutical Reviewer

45

Please note that the sponsor's proposed omissions are indicated by strikeovers, inclusions by underlined text.

15 Page(s) Withheld

_____ Trade Secret / Confidential

✓ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Administrative- 1a

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/s/

Dawn McNeil
2/3/05 01:05:15 PM
MEDICAL OFFICER

Rigoberto Roca
2/3/05 01:22:16 PM
MEDICAL OFFICER

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/s/

Kimberly Compton
2/4/05 08:45:21 PM
CSO

Office of Drug Safety

Memo

To: Bob Rappaport, M.D.
Director, Division of Anesthetic, Critical Care and Addiction Drug Products, HFD-170

From: Denise Toyer, Pharm.D.
Deputy Director, Division of Medication Errors and Technical Support, HFD-420

Through: Carol Holquist, R.Ph.
Director, Division of Medication Errors and Technical Support, HFD-420

cc: Kim Compton
Project Manager, Division of Anesthetic, Critical Care and Addiction Drug Products, HFD-170

Date: January 27, 2005

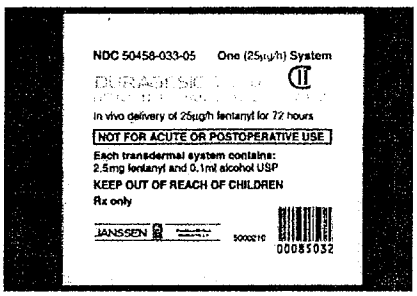
Subject: ODS Consult 03-0035-1; NDA 19-813/S-039
Duragesic (Fentanyl Transdermal System) 12 mcg/hr

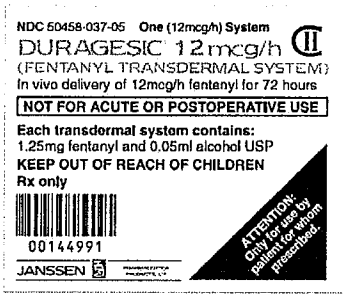
This memorandum is in response to the December 12, 2004 request from your Division for a review of the Duragesic 12 mcg/hr Pouch label, System Print Mat, Carton and Insert labeling. This supplement provides for the addition of a new strength to the Duragesic Product Line. This new strength is not intended for use as initial therapy but to allow for dose adjustment, if a smaller dose adjustment is indicated. Currently the lowest marketed strength of Duragesic is 25 mcg/hr.

DMETS conducted a search of the FDA's Adverse Event Reporting System (AERS) for any medication error reports involving potential name confusion between Duragesic and other proprietary names or any reports involving medication errors resulting from confusing Duragesic labels and labeling. The MEDDRA Preferred Terms (PT): "Medication Error, Accidental Overdose, and Overdose NOS" and the product name "Duragesic" were used as search criteria. The AERS search did not identify any medication error reports resulting from confusing labels and labeling. The majority of the medication error reports involved misuse/abuse of the patch (e.g., chewing or withdrawing the contents into a syringe) and complaints relating to the recall of Duragesic 75 mcg/hr. These issues have been addressed in several reviews conducted by Safety Evaluators in the Division of Drug Risk Evaluation and thus will not be discussed in this review.

In the review of the Pouch label, System Print Mat, Carton and Insert labeling of Duragesic 12 mcg/hr Transdermal System, DMETS has attempted to focus on safety issues relating to possible medication errors. DMETS has identified the following area of possible improvement, which might minimize potential user error.

We note that the colors used on the primary display panel for the 12 mcg/hr and 25 mcg/hr systems are nearly identical (see below). Although one is [redacted] the similarity in colors may increase the potential for selection errors. We recommend that two distinguishing colors be used to prevent the potential for confusion.





In summary, DMETS recommends implementation of the labeling revisions outlined above that might lead to safer use of Duragesic. We would be willing to revisit these issues if the Division receives another draft of the labeling from the manufacturer.

If you have any questions or need clarification, please contact Sammie Beam at 301-827-3242.

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/s/

Denise Toyer
1/27/05 02:55:38 PM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
1/27/05 03:01:02 PM
DRUG SAFETY OFFICE REVIEWER

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/s/

Denise Toyer
1/27/05 02:55:38 PM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
1/27/05 03:01:02 PM
DRUG SAFETY OFFICE REVIEWER

nulldate
DRUG SAFETY OFFICE REVIEWER

FDA 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

MEMORANDUM

DATE: 02/04/05

TO: Rigoberto Roca, M.D., Deputy Division Director, DACCADP

FROM: D. Elizabeth McNeil, M.D., Medical Officer, DACCADP

RE: NDA 19-813 Serial No.: 039

At the time of my NDA review, financial disclosure information on this submission was still pending.

Subsequent to the completion of my review, we received the pending data.

I have reviewed the financial disclosure information provided and all is in order. There do not appear to have been any financial arrangements with investigators that could have biased the study.

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/s/

Dawn McNeil
2/4/05 04:40:33 PM
MEDICAL OFFICER

Rigoberto Roca
2/4/05 05:16:08 PM
MEDICAL OFFICER
I concur with Dr. McNeil's assessment.