CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

19-813/S033

Trade Name: Duragesic

Generic Name: Fentanyl

Sponsor: ALZA Corporation

Approval Date: 2/7/2008

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-813/S033

CONTENTS

Reviews / Information Included in this NDA Review.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-813/S033

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 19-813/S-033

Johnson & Johnson Pharmaceutical Research & Development, L.L.C.
(c/o) ALZA Corporation
920 Route 202 South
P.O. Box 300
Raritan, NJ 08869-0602

Attention: Michael H. Kaufman
Director, Regulatory Affairs

Dear Mr. Kaufman:

Please refer to your supplemental new drug application dated January 12, 2001, received January 16, 2001, 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 February 11, 2002, September 9, 2005, June 22, and December 14, 2007.

Your submission of September 9, 2005 constituted a complete response to our September 26, 2001 action letter.

This "Changes Being Effected" supplemental new drug application originally provided for changes only to the Pouchstock. Supplement S-043, submitted March 19, 2007, provides for changes to the Package Insert, Medication Guide, Carton, Pouchstock, and the Risk Management Plan. In the final stages of labeling negotiations, the Package Insert, Carton, Information for Use, and Medication Guide were also submitted to Supplement S-033. The Risk Management Plan is currently under review as part of Supplement S-043.

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 enclosed content of labeling [21 CFR 314.50(1)] in structured product labeling (SPL) format submitted on December 14, 2007, and with the following editorial revision to the Medication Guide as agreed upon in an email exchange with Michael Kaufman of Johnson and Johnson on January 15, 2008.

What are the possible side effects of DURAGESIC®?

"Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088."

CONTENT OF LABELING

We will transmit the content of labeling in SPL format, as amended, to the National Library of Medicine for public dissemination.

CARTON AND IMMEDIATE CONTAINER LABELS

We acknowledge your December 14, 2007 electronic submission containing the representative mock-up of the 50mcg/hr printed Carton and Pouchstock labels.

Submit final printed carton and container labels that are identical to the enclosed Carton and Pouchstock labels for all strengths as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (October 2005)*. Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Final Printed Carton and Container Labels for approved NDA 19-813/S-033**." Approval of this submission by FDA is not required before the labeling is used.

Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

LETTERS TO HEALTH CARE PROFESSIONALS

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

MedWatch
Food and Drug Administration
HFD-001, Suite 5100
5515 Security Lane
Rockville, MD 20852

REPORTING REQUIREMENTS

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 Kathleen Davies, Regulatory Project Manager, at (301) 796-2205.

Sincerely,

{See appended electronic signature page}

Bob Rappaport, M.D.
Director
Division of Anesthesia, Analgesia
and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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

2/7/2008 09:54:40 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-813/S033

OTHER ACTION LETTER(s)

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug
Administration
Rockville MD 20857

NDA 19-813/S-033

Alza Corporation
1900 Charleston Road
P. O. Box 7210
Mountain View, CA 94039-7210

Attention: Janne Wissel
Sr. Vice President, Operations

Dear Ms. Wissel:

Please refer to your supplemental new drug application dated January 12, 2001, received January 16, 2001, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Duragesic (fentanyl transdermal system).

This "Changes Being Effected" supplemental new drug application provides for the following changes to the 25 µg/h, 50 µg/h, 75 µg/h and 100 µg/h (b) (4)) pouch stocks:

1. Addition of the bolded statement "KEEP OUT OF REACH OF CHILDREN" to the front of the (b) (4) pouch stock.

2. Removal of the statement (b) (4) from the front of the (b) (4) pouch stock.

3. Removal of the statement (b) (4) from the front of the (b) (4) pouch stock.

4. Addition of the statement "Rx Only" to the front of the (b) (4) pouch stock.

5. Update of the code number on the front of the (b) (4) pouch stock.

6. Addition of instructions stating: (b) (4) on the right side of the (b) (4) pouch stock.

7. Change of Alza Corporation address from "Palo Alto, CA 94034" to "Mountain View, CA 94043"

We have completed the review of this application, and it is approvable. Before this application may be approved, however, it will be necessary for you to submit final printed labeling (FPL) revised as follows:

Include the following paragraph in the labeling of the pouch stock:

> BECAUSE SERIOUS OR LIFE-THREATENING HYPOVENTILATION COULD OCCUR, DURAGESIC (FENTANYL TRANSDERMAL SYSTEM) IS CONTRAINDICATED:
> - In the management of acute or post-operative pain, including use in out-patient surgeries.
> - In the management of mild or intermittent pain responsive to PRN or non-opioid therapy.
> - In doses exceeding 25 mcg/h at the initiation of the opioid therapy.

In addition, all previous revisions as reflected in the most recently approved labeling must be included. To facilitate review of your submission, please provide a highlighted or marked-up copy that shows the changes that are being made.

Please submit the copies of final printed labeling (FPL) electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA* (January 1999). Alternatively, you may submit 20 paper copies of the FPL, ten of which individually mounted on heavy weight paper or similar material.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

Within 10 days after the date of this letter, you are required to amend the supplemental application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

If you have any questions, call Judit Milstein, Regulatory Project Manager, at (301) 827-7440.

Sincerely,

{See appended electronic signature page}

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

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

/s/

Cynthia McCormick

9/26/01 06:52:29 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-813/S033

LABELING

DURAGESIC®
(FENTANYL
TRANSDERMAL
SYSTEM) CII

Rx only

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 all cytochrome P450 3A4 inhibitors (such as ritonavir, ketoconazole, itraconazole, troleandomycin, clarithromycin, nelfinavir, nefazodone, amiodarone, amprenavir, aprepitant, diltiazem, erythromycin, fluconazole, fosamprenavir, grapefruit juice, and verapamil) 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 any CYP3A4 inhibitor 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.

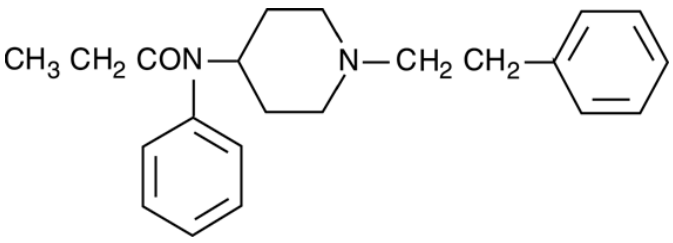
Persons at increased risk for opioid abuse include those with a personal or family history of substance abuse (including drug or alcohol abuse or addiction) or mental illness (e.g., major depression). Patients should be assessed for their clinical risks for opioid abuse or addiction prior to being prescribed 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. Do not use a 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 the patient or caregiver to the contents of the patch, which can result in an overdose of fentanyl that may be fatal.

Avoid exposing the DURAGESIC® application site and surrounding area to direct external heat sources, such as heating pads or electric blankets, heat or tanning lamps, saunas, hot tubs, and heated water beds, while wearing the system. Avoid taking hot baths or sunbathing. There is a potential for temperature-dependent increases in fentanyl released from the system resulting in possible overdose and death. Patients wearing DURAGESIC® systems who develop fever or increased core body temperature due to strenuous exertion should be monitored for opioid side effects and the DURAGESIC® dose should be adjusted if necessary.

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

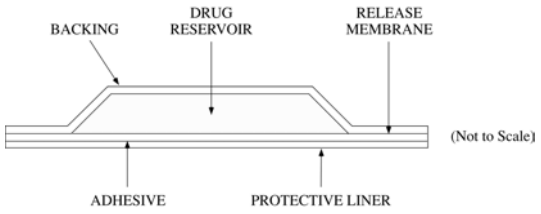
The amount of fentanyl released from each system per hour is proportional to the surface area (25 mcg/h per 10 cm^2). The composition per unit area of all system sizes is identical. Each system also contains 0.1 mL of alcohol USP per 10 cm^2.

Dose* (mcg/h)	Size (cm^2)	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.

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).

The kinetics of fentanyl in normal subjects following application of a 100 mcg/hr DURAGESIC® patch were bioequivalent with or without a Bioclusive™ overlay (polyurethane film dressing).

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)

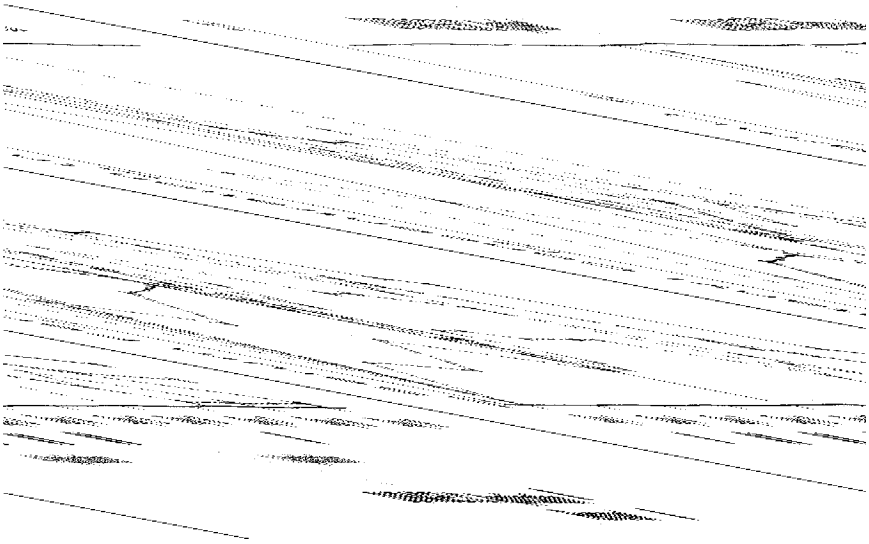


TABLE A: FENTANYL PHARMACOKINETIC PARAMETERS FOLLOWING FIRST 72-HOUR APPLICATION OF DURAGESIC®

	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 $t_{1/2}$ (h) Range
Surgical Patients	27 – 75	3 - 8	3 - 12
Hepatically Impaired Patients	3 - 80+	0.8 - 8+	4 - 12+
Renally Impaired Patients	30 – 78	–	–

+Estimated

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

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

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.

Special Populations

Hepatic or Renal Disease

Insufficient information exists to make recommendations regarding the use of DURAGESIC® in patients with impaired renal or hepatic function. Fentanyl is metabolized primarily via human cytochrome P450 3A4 isoenzyme system and mostly eliminated in urine. If the drug is used in these patients, it should be used with caution because of the hepatic metabolism and renal excretion of fentanyl.

Pediatric Use

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.

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.

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.

DURAGESIC® should be used with caution in elderly, cachectic or debilitated patients as they may have altered pharmacokinetics due to poor fat stores, muscle wasting, or altered clearance (see **DOSAGE AND ADMINISTRATION**).

Drug Interactions

The interaction between ritonavir, a CPY3A4 inhibitor, 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**, **PRECAUTIONS** and **DOSAGE AND ADMINISTRATION).**

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 CYP3A4 activity may reduce the efficacy of DURAGESIC®. The concomitant use of transdermal fentanyl with all CYP3A4 inhibitors (such as ritonavir, ketoconazole, itraconazole, troleandomycin, clarithromycin, nelfinavir, nefazadone, amiodarmone, amprenavir, aprepitant, diltiazem, erythromycin, fluconazole, fosamprenavir, grapefruit juice, and verapamil) 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 any CYP3A4 inhibitor should be carefully monitored for an extended period of time and dosage adjustments should be made if warranted (see **BOX WARNING, WARNINGS**, **PRECAUTIONS**, and **DOSAGE AND ADMINISTRATION** for further information).

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. Do not use a 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 the patient or caregiver to the contents of the patch, which can result in an overdose of fentanyl that may be fatal.

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 and surrounding area to direct external heat sources, such as heating pads or electric blankets, heat or tanning lamps, saunas, hot tubs, and heated water beds, etc., while wearing the system. Patients should be advised against taking hot baths or sunbathing. There is a potential for temperature-dependent increases in fentanyl released from the system resulting in possible overdose and death.

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. **Patients wearing DURAGESIC® systems who develop fever or increased core body temperature due to strenuous exertion should be monitored for opioid side effects and the DURAGESIC® dose should be adjusted if necessary.**

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 transdermal fentanyl with all CYP3A4 inhibitors (such as ritonavir, ketoconazole, itraconazole, troleandomycin, clarithromycin, nelfinavir, nefazadone, amiodarone, amprenavir, aprepitant, diltiazem, erythromycin, fluconazole, fosamprenavir, grapefruit juice, and verapamil) 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 any CYP3A4 inhibitor 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.

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 – Discontinuation of DURAGESIC®).**

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

Patients and their caregivers should be provided with a Medication Guide each time DURAGESIC® is dispensed because new information may be available.

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 the patch is cut, damaged, or changed in any way. Using a patch that is cut, damaged, or changed in any way can expose the patient or caregiver to the contents of the patch, which can **result in an overdose of fentanyl that may be fatal**.
   - 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 the dose of DURAGESIC® or the number of patches applied to the skin should NEVER be adjusted without the prescribing healthcare professional's instruction.

6. Patients should be advised that while wearing the patch, they should avoid exposing the DURAGESIC® application site and surrounding area to direct external heat sources, such as:

   - heating pads,
   - electric blankets,

- sunbathing,
- heat or tanning lamps,
- saunas,
- hot tubs or hot baths, and
- heated water beds, etc.

7. Patients should also be advised of a potential for temperature dependent increases in fentanyl release from the patch that could result in an overdose of fentanyl; therefore, patients who develop a high fever or increased body temperature due to strenuous exertion while wearing the patch should contact their physician.

8. Patients should be advised that if they experience problems with adhesion of the DURAGESIC® patch, they may tape the edges of the patch with first aid tape. If problems with adhesion persist, patients may overlay the patch with a transparent adhesive film dressing (e.g., Bioclusive™ or Tegaderm™).

9. Patients should be advised that if the patch falls off before 72 hours a new patch may be applied to a different skin site.

10. 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.

11. 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.

12. 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).

13. 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.

14. 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.

15. Patients should be advised to consult their physician or pharmacist if other medications are being or will be used with DURAGESIC®.

16. Patients should be advised of the potential for severe constipation.

17. 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.

18. Patients should be advised that DURAGESIC® contains fentanyl, a drug with high potential for abuse.

19. Patients, family members and caregivers should be advised to protect DURAGESIC® from theft or misuse in the work or home environment.

20. 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**.

21. 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.

22. Patients should be informed that, if the patch dislodges and accidentally sticks to the 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.

23. 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.

24. 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®.

25. Patients should be informed that accidental exposure or misuse may lead to death or other serious medical problems.

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 CYP3A4 activity may reduce the efficacy of DURAGESIC®. The concomitant use of transdermal fentanyl with all CYP3A4 inhibitors (such as ritonavir, ketoconazole, itraconazole, troleandomycin, clarithromycin, nelfanivir, nefazadone, amiodarone, amprenavir, aprepitant, diltiazem, erythromycin, fluconazole, fasamprenavir, grapefruit juice, and verapamil) may result in an increase in fentanyl plasma concentrations, which could increase or prolong adverse drug effects and may cause fatal respiratory depression. Patients receiving DURAGESIC® and any CYP3A4 inhibitor 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, WARNINGS,** and **DOSAGE AND ADMINISTRATION** for further information).

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.

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.

DURAGESIC® should be used with caution in elderly, cachectic, or debilitated patients as they may have altered pharmacokinetics due to poor fat stores, muscle wasting or altered clearance (see **DOSAGE AND ADMINISTRATION**).

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. Do not use a 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 the patient or caregiver to the contents of the patch, which can result in an overdose of fentanyl that may be fatal.

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. The DURAGESIC® patch should not be used 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 the patient or caregiver to the contents of the patch, which can result in an overdose of fentanyl that may be fatal.

Each DURAGESIC® patch 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.

If problems with adhesion of the DURAGESIC® patch occur, the edges of the patch may be taped with first aid tape. If problems with adhesion persist, the patch may be overlayed with a transparent adhesive film dressing (e.g., Bioclusive™ or Tegaderm™).

If the patch falls off before 72 hours, dispose of it by folding in half and flushing down the toilet. A new patch may be applied to a different skin site.

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 all cytochrome P450 3A4 inhibitors (such as ritonavir, ketoconazole, itraconazole, troleandomycin, clarithromycin, nelfinavir, nefazodone, amiodarone, amprenavir, aprepitant, diltiazem, erythromycin, fluconazole, fosamprenavir, grapefruit juice, and verapamil) 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 any CYP3A4 inhibitor 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, WARNINGS, and PRECAUTIONS for further information).

Pediatric patients converting to DURAGESIC® with a 25 mcg/h patch should be opioid-tolerant and receiving at least 60 mg of oral morphine or the equivalent 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**).

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.

DURAGESIC® should be used with caution in elderly, cachectic, or debilitated patients as they may have altered pharmacokinetics due to poor fat stores, muscle wasting, or altered clearance (see **CLINICAL PHARMACOLOGY – Special Populations, Geriatric Use**).

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.

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.

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[1,a] EQUIANALGESIC POTENCY CONVERSION

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

[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	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®).**

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 (cm^2)	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 use a 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 the patient or caregiver to the contents of the patch, which can result in an overdose of fentanyl that may be fatal.

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**.

Bioclusive™ is a trademark of Ethicon, Inc.
Tegaderm™ is a trademark of 3M

A schedule CII narcotic. DEA order form required.

Manufactured by:
ALZA Corporation
Mountain View, CA 94043

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

[Add new code post-approval]

[Revised Month Year]

Medication Guide

DURAGESIC®
(FENTANYL TRANSDERMAL SYSTEM) CII

(Dur-ah-GEE-zik)

IMPORTANT:

- **Keep DURAGESIC® in a safe place away from children and pets. Accidental use by a child or pet is a medical emergency and may result in death. If a child or pet accidentally uses DURAGESIC®, get emergency help right away.**
- **Make sure you read the separate "Instructions for Applying a DURAGESIC® Patch." Always use a DURAGESIC® Patch the right way. DURAGESIC® can cause serious breathing problems and death, especially if it is used the wrong way.**
- **DURAGESIC® is a federally controlled substance (C-II) because it can be abused. Keep DURAGESIC® in a safe place to prevent theft. Selling or giving away DURAGESIC® may harm others, and is against the law.**
- **Tell your doctor if you (or a family member) have ever abused or been dependent on alcohol, prescription medicines or street drugs.**

Read the Medication Guide that comes with DURAGESIC® before you start using it and each time you get a new prescription. There may be new information. This Medication Guide does not take the place of talking to your healthcare provider about your medical condition or your treatment. Make sure you read and understand all the instructions for using DURAGESIC®. Do not use DURAGESIC® unless you understand everything. Talk to your healthcare provider if you have questions.

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

DURAGESIC® is a skin patch that contains fentanyl. **Fentanyl is a very strong opioid narcotic pain medicine that can cause serious and life-threatening breathing problems. Serious and life-threatening breathing problems can happen because of an overdose or if the dose you are using is too high for you. Call your doctor right away or get emergency medical help if you:**

- have trouble breathing, or have slow or shallow breathing
- have a slow heartbeat
- have severe sleepiness
- have cold, clammy skin
- feel faint, dizzy, confused, or cannot think, walk, or talk normally
- have a seizure
- have hallucinations

DURAGESIC® is only for adults and children over the age of two with persistent, moderate to severe chronic pain and who:

- are already using another strong opioid narcotic pain medicine around-the-clock, and have been using the medicine regularly for a week or longer. This is called being opioid-tolerant
- have pain that cannot be controlled with other medicines

Do not use DURAGESIC®:

- **if you are not already using another opioid narcotic medicine and are not opioid tolerant**
- 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
- if you have asthma symptoms or have severe asthma

A DURAGESIC® 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 get medical care for them right away.

DURAGESIC® patch is not safe for everyone. Tell your doctor about all of your medical conditions.

Tell your doctor if you are planning to become pregnant, are pregnant, or breastfeeding. DURAGESIC® may cause serious harm to a baby.

Tell your doctor about all the medicines you take. Some medicines may cause serious or life-threatening side effects when used with DURAGESIC®. Your doctor will tell you if it is safe to take other medicines while you are using DURAGESIC®.

Know the medicines you take. Keep a list of your medicines to show to your doctor and pharmacist.

How should I use DURAGESIC®?

Read the separate "Instructions for Applying a DURAGESIC® Patch.

- **You must always use** DURAGESIC® patches the right way:
  - **Do not** use a DURAGESIC® patch if the seal is broken, or the patch is cut, damaged, or changed in any way.
  - **Do not** use heat sources such as heating pads, electric blankets, heat lamps, tanning lamps, saunas, hot tubs, or heated waterbeds while wearing a DURAGESIC® patch.
  - **Do not** take hot baths or sunbathe while wearing a DURAGESIC® patch.
- **If you have problems with the DURAGESIC® patch not sticking:**
  1. Apply first aid tape only to the edges of the patch.
  2. If problems with the patch not sticking persist, cover the patch with Bioclusive™ or Tegaderm™. These are special see-through adhesive dressings. **Never cover a DURAGESIC® patch with any other bandage or tape**.
- **If your DURAGESIC® patch falls off before 3 days or 72 hours, fold the sticky side together and flush down a toilet. Put a new one on at a different skin site.**
- **Do not change your dose unless your doctor tells you to.** Your doctor may change your dose after seeing how the medicine affects you. Do not use DURAGESIC® more often than prescribed. Call your doctor if your pain is not well controlled while using DURAGESIC®.
- **Do not stop using DURAGESIC® suddenly.** Stopping DURAGESIC® suddenly can make you sick with withdrawal symptoms (for example, nausea, vomiting, diarrhea, anxiety, and shivering). Your body can develop a physical dependence on DURAGESIC®. If your doctor 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 doctor.
- **Do not wear more than one DURAGESIC® patch at a time,** unless your doctor tells you to do so.
- **Call your doctor right away if**
  - **You get a fever higher than 102°F**
  - Your body temperature increases from exercise

  A fever or increase in body temperature may cause too much of the medicine in DURAGESIC® to pass into your body.

- **If you use more DURAGESIC® than your doctor has prescribed, get emergency medical help right away.**

- **Do not drink any alcohol while using DURAGESIC®.** Alcohol can increase your chances of having serious 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 doctor to tell you when it is okay to do these activities.

- When you remove your DURAGESIC® patch, fold the sticky sides of a used DURAGESIC® patch together and flush it down the toilet. **Do not put used DURAGESIC® patches in a trash can.**

What are the possible side effects of DURAGESIC®?

Serious side effects include:

- **Life-threatening breathing problems.** See "What is the most important information I should know about DURAGESIC®?"
- **Low blood pressure.** 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, sweating, and pain and redness where the patch was applied.

Constipation is a very common side effect of all opioid medicines. Talk to your doctor about the use of laxatives and stool softeners to prevent or treat constipation while taking DURAGESIC®.

Talk to your healthcare provider about any side effect that concerns you.

These are not all the possible side effects of DURAGESIC®. For a complete list, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store DURAGESIC®?

- Store DURAGESIC® below 77° F (25° C).
- Keep a DURAGESIC® patch in its protective pouch until you are ready to use it.
- **Keep DURAGESIC® in a safe place out of the reach of children and pets.**
- Dispose of DURAGESIC® patches you no longer need. Open the unused packages, fold the sticky sides of the patches together, and flush them down the toilet.

General information about the safe and effective use of DURAGESIC®

- 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.**
- This Medication Guide summarizes the most important information about DURAGESIC®. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about DURAGESIC® that is written for doctors.

For questions about DURAGESIC®, call the Ortho-McNeil Janssen Scientific Affairs Customer Communications Center at 1-800-526-7736. If this is a medical emergency, please call 911.

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.

This Medication Guide has been approved by the United States Food and Drug Administration.

Bioclusive™ is a trademark of Ethicon, Inc.
Tegaderm™ is a trademark of 3M

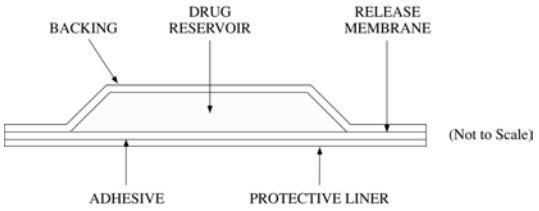
Manufactured by:
ALZA Corporation
Mountain View, CA 94043

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

[Add new code post-approval]
[Revised Month Year]

DURAGESIC® (Dur-ah-GEE-zik)
(fentanyl transdermal system) CII

Instructions for Applying a DURAGESIC® patch



Before Applying DURAGESIC®

- **DURAGESIC® is a patch with a medicine gel sealed inside. The patch is designed to keep the medicine gel from getting on your hands or body. If the gel from the patch accidentally gets on your skin, wash the area with large amounts of water only. Do not use soap, alcohol, lotions, oils, or other products to remove the medicine gel because they may increase the medicine's ability to go through the skin.**

- **Each DURAGESIC® patch is sealed in its own protective pouch. Do not remove a DURAGESIC® patch from the pouch until you are ready to use it.**

- **Do not use a DURAGESIC® patch if the seal is broken or the patch is cut, damaged or changed in any way.**

- **DURAGESIC® patches are available in 5 different doses and patch sizes. Make sure you have the right dose patch or patches that have been prescribed for you.**

Applying a DURAGESIC® Patch

1. **Skin Areas Where the DURAGESIC® Patch May Be Applied:**

   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 (see Figures 1-4).

   For children (and adults with mental impairment):

   - **Put the patch on the upper back (see Figure 2).** This will lower the chances that the child will remove the patch and put it in their mouth.

   For adults and children

   - Do not put a DURAGESIC® patch on skin that is very oily, burned, broken out, cut, irritated, or damaged in any way.
   - 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 (see Figure 5).
   - **Talk to your doctor if you have questions about skin application sites.**

Figure 1

Figure 2

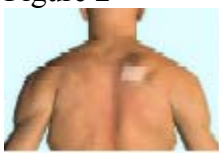


Figure 3

Figure 4

Figure 5

2. **Prepare to Apply a DURAGESIC® Patch:**
   - Choose the time of day that is best for you to apply DURAGESIC®. Change it at about the same time of day (3 days or 72 hours after you apply the patch) or as directed by your doctor.
   - Do not wear more than one DURAGESIC® patch at a time unless your doctor tells you to do so. Before putting on a new DURAGESIC® patch, remove the patch you have been wearing.
   - Clean the skin area with clear water **only**. **Pat skin completely dry.** Do not use anything on the skin such as soaps, lotions, oils, or alcohol before the patch is applied.

3. **Tear open** the pouch along the dotted line, starting at the slit, and remove a DURAGESIC® patch. 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 (see Figure 6).

Figure 6

4. **Peel:** Peel the liner from the back of the patch and throw away. **Touch the sticky side of a DURAGESIC® patch as little as possible** (see Figure 7).

Figure 7

5. **Press:** Press the patch onto the chosen skin site **with the palm of your hand and hold there for at least 30 seconds** (see Figure 8). Make sure it sticks well, especially at the edges.

Figure 8

- DURAGESIC® may not stick to all patients. You need to check the patches often to make sure that they are sticking well to the skin.
- If the patch falls off right away after applying, throw it away and put a new one on at a different skin site (see Disposing a DURAGESIC® patch).
- If you have a problem with the patch not sticking
  - Apply first aid tape only to the edges of the patch.
  - If you continue to have problems with the patch sticking, you may cover the patch with Bioclusive™ or Tegaderm™. These are special see-through adhesive dressings. **Never cover a DURAGESIC® patch with any other bandage or tape**. Remove the backing from the Bioclusive™ or Tegaderm™ dressing and place it carefully over the DURAGESIC® patch, smoothing it over the patch and your skin.

- **If your patch falls off later, but before 3 days (72 hours) of use, discard it properly (see Disposing a DURAGESIC® patch) and put a new one on at a different skin site. Be sure to let your doctor know that this has happened, and do not replace the new patch until 3 days (72 hours) after you put it on (or as directed by your doctor).**

6. Wash your hands when you have finished applying a DURAGESIC® patch.

7. Remove a DURAGESIC® patch after wearing it for 3 days (72 hours) (see "Disposing of DURAGESIC®"). Choose a **different** place on the skin to apply a new DURAGESIC® patch and repeat Steps 2 through 6.

   Do not apply the new patch to the same place as the last one.

Water and DURAGESIC®

- You can bathe, swim or shower while you are wearing a DURAGESIC® patch. If the patch falls off before 3 days (72 hours) after application, discard it properly (see Disposing a DURAGESIC® patch) and put a new one on at a different skin site. Be sure to let your doctor know that this has happened, and do not replace the new patch until 3 days (72 hours) after you put it on (or as directed by your doctor).

Disposing a DURAGESIC® Patch

- Fold the used DURAGESIC® patch in half so that the sticky side sticks to itself (Figure 9). **Flush the used DURAGESIC® down the toilet right away** (Figure 10). **A used DURAGESIC® patch CAN be VERY 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 trashcan.

Figure 9

Figure 10

Bioclusive™ is a trademark of Ethicon, Inc.

Tegaderm™ is a trademark of 3M

Rx Only

Manufactured by:
ALZA Corporation
Mountain View, CA 94043

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

Date Component Code

SLIT WIDTH 16.25"

FRONTS

BACKS

5.0"

4.0625"

.5" x .25"EYEMARK

(b) (4)

NDC 50458-034-05 One (50mcg/h) System

DURAGESIC® 50mcg/h

(FENTANYL TRANSDERMAL SYSTEM)

In vivo delivery of 50mcg/h fentanyl for 72 hours

Because it can cause trouble breathing which can be fatal, DO NOT USE DURAGESIC®:
- For short term or any post-operative pain, or occasional pain
- For mild pain or pain that can be treated with non-opioid or as-needed opioid medication
- Unless you have been using other narcotic opioid medicines (must be opioid tolerant)

Each transdermal system contains:
5mg fentanyl and 0.2mL alcohol USP

KEEP OUT OF REACH OF CHILDREN

Read enclosed DURAGESIC® Medication Guide for important safety information.

(01)30050458034059

FPO

Janssen L.P.

Rx only

ONLY for pain requiring opioid medicine around-the-clock

To open, tear along dotted line from slit.
(DO NOT CUT)

Inactive Ingredients: Hydroxyethyl cellulose, ethylene vinyl-acetate copolymer, silicone adhesive between polyester backings.

Dosage: For information for use, see accompanying product literature.

Apply immediately upon removal from pouch and after removal of the protective liner. Do not expose area to heat. Do not store unpouched or above 77°F (25°C).

DO NOT USE IF SEAL ON POUCH IS BROKEN

See Medication Guide for important safety information.

Manufactured by:
ALZA Corporation
Mountain View, CA 94043
Mock Up Dec 2007

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

CONTROL
EXP. DATE

00000000MU

DURAGESIC® 50 mcg/h CII
(FENTANYL TRANSDERMAL SYSTEM)

NDC 50458-034-05 **Five** (50mcg/h) **Systems**

DURAGESIC® 50 mcg/h CII
(FENTANYL TRANSDERMAL SYSTEM)

In vivo delivery of 50mcg/h fentanyl for 72 hours

Because it can cause trouble breathing which can be fatal, DO NOT USE DURAGESIC®:
- **For short term or any post-operative pain, or occasional pain**
- **For mild pain or pain that can be treated with non-opioid or as-needed opioid medication**
- **Unless you have been using other narcotic opioid medicines (must be opioid tolerant)**

Each transdermal system contains: 5mg fentanyl and 0.2mL alcohol USP
DO NOT USE IF SEAL ON POUCH IS BROKEN
KEEP OUT OF REACH OF CHILDREN
Read enclosed DURAGESIC® Medication Guide for important safety information.

Rx only

ONLY for pain requiring opioid medicine around-the-clock

Janssen L.P.

CONTROL
EXP. DATE

Inactive Ingredients: Hydroxyethyl cellulose, ethylene vinyl-acetate copolymer, silicone adhesive between polyester backings.

Dosage: For information for use, see accompanying product literature.

Apply immediately upon removal from pouch and after removal of the protective liner. Do not expose area to heat. Do not store unpouched or above 77°F (25°C).

See Medication Guide for important safety information.

For your convenience in recording narcotic use,
INITIAL/DATE

1. _____ 2. _____ 3. _____
4. _____ 5. _____

NSN#6505-01-335-9390

For questions about DURAGESIC®, call the Ortho-McNeil Janssen Scientific Affairs Customer Communications Center at 1-800-526-7736.
If this is a medical emergency, please call 911.

Manufactured by:
ALZA Corporation
Mountain View, CA 94043

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

ONLY for pain requiring opioid medicine around-the-clock

Janssen L.P.

FPO

(b) (4)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-813/S033

OTHER REVIEW(S)

MEMORANDUM	Division of Medication Errors and Technical Support Office of Surveillance and Epidemiology WO 22, Mailstop 4447, HFD-420 Center for Drug Evaluation and Research

To: Bob Rappaport, MD
Director, Division of Anesthesia, Analgesia, and Rheumatology Products

Through: Alina Mahmud, RPh, MS, Team Leader
Denise Toyer, PharmD, Deputy Director
Carol Holquist, RPh, Director
Division of Medication Errors and Technical Support, HFD-420

From: Kimberly Pedersen, RPh, Safety Evaluator
Division of Medication Errors and Technical Support, HFD-420

Date: October 18, 2006

Subject: OSE Review 2006-540
Duragesic (Fentanyl Transdermal System)
12.5 mcg/hr, 25 mcg/hr, 50 mcg/hr, 75 mcg/hr, and 100 mcg/hr
NDA 19-813/ S-033

This memorandum is in response to an October 06, 2006 request from your Division for a review of the proposed changes to the package insert and pouch labeling for Duragesic. The supplement provides for changes to the foil overwrap labeling. However, the Division also plans to update the package insert as a part of this supplement. These package insert changes include, but are not limited to the addition of drug interaction information with moderate cytochrome P450 3A4 inhibitors, pharmacokinetic data in geriatric patients, and issues relating to the patch (e.g., exposure of the patch to direct external heat sources/fever and patch adhesion warnings). The issues with the patch were concerns that DMETS raised in our previous post-marketing consult (05-0152, 2005).

A. GENERAL COMMENTS

1. We note the addition of the boxed warning statement in the insert labeling with regard to the effects of internal and external heat sources on the patch. However, this warning does not appear on the actual patch, overwrap, or container labels/labeling. As found in post-marketing reports, there appears to be a lack of knowledge for patients and practitioners to the effects of heat on the release of fentanyl from the patch. This lack of knowledge has resulted in adverse events and fatalities related to the use/abuse of fentanyl patches. DMETS continues to recommend the addition of this warning statement to the patch (e.g. Do not use with or expose to heat). However, as space on the actual patch is limited, DMETS recommends adding a warning statement to the outer packaging, which includes the foil overwrap and outer box. This will serve to educate practitioners and patients, as it would be impossible to assure all users will review the updated insert labeling.

2. Since post-marketing reports have found that patients who were exposed to external elevated temperatures (e.g. while gardening) or performed strenuous work-outs appear to have symptoms suggesting elevated fentanyl levels, DMETS suggests expanding the “fever” warning found in the Black box, Warnings, and Precautions, Information to Patients Sections to include these exposures. Thus, hot conditions (elevated external temperatures) and/or strenuous activities may lead to elevated core body temperature and increase the cutaneous vasodilation/perfusion with potentially resultant elevated fentanyl absorption.

3. DMETS notes the heat exposure warning describes avoiding “direct” heating sources, but post-marketing reporting suggests exposure in close proximity to the patch could also result in elevated release of

fentanyl. One particular case notes a nurse applied a heating pad near the patch application site that resulted in symptoms of overdose. Thus, please revise the warning to read "Avoid exposing the Duragesic application site and surrounding area to external heat…"

4. Due to the multitude of post-marketing reports that indicate concurrent use of multiple patches that appear to have resulted in the patients death, DMETS suggests the addition of a warning about the use of multiple patches without physician supervision potentially leading to overdose and adverse reactions/death in the 'Information for Patients' and the 'Dosage and Administration' sections.

B. BLACK BOX WARNING

DMETS recommends the inclusion of grapefruit juice in the moderate cytochrome P450 3A4 warning statement as documented in the 'Drug Interaction' Subsection of the insert for consistency and to assure that practitioners and patients are aware of this interaction. The black box warning is more commonly referenced by practitioners; thus, the inclusion of these data will help assure the dissemination of this information.

C. CLINICAL PHARMACOLOGY, Pharmacokinetics Subsection

The second sentence "There is the potential…." suggests that the patient should not use an overlay. If so, please state as such for clarity. However, if not, please document the type of overlay (e.g. Tegaderm) and length of time allowed for use that has been found to result in fewer adverse reactions, if appropriate.

D. PRECAUTIONS (Information to Patients)

1. In item number seven, the second sentence "Due to the potential …." suggests the sponsor is recommending that the patient can use an overlay, which is different from the statement in the Clinical Pharmacology section. If the sponsor is suggesting an overlay is appropriate, please state as such and document the type/brand/size (e.g. Tegaderm) of overlay and the length of time allowed for use that has been found to result in fewer adverse reactions, otherwise revise the sentence.

2. Consider adding a statement advising patients not to use Duragesic concomitantly with grapefruit juice to assure the patients are aware of the food-drug interaction. These interactions may go overlooked in patient counseling.

3. Item numbers nine and twenty-three appear to be identical. Therefore, one of these statements should be deleted.

E. Dosing and Administration

See Comment D 1.

We would be willing to meet with the Division for further discussion if needed. If you have any questions or need clarification, please contact DMETS Project Manager, Diane Smith at 301-796-0538.

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

/s/

Kimberly Culley-Pedersen
10/27/2006 01:00:08 PM
DRUG SAFETY OFFICE REVIEWER

Alina Mahmud
10/27/2006 01:47:57 PM
DRUG SAFETY OFFICE REVIEWER

Denise Toyer
10/27/2006 01:56:02 PM
DRUG SAFETY OFFICE REVIEWER
Also signing for Carol Holquist, DMETS Director, in her absence

Division of Anesthetic, Critical Care, and Addiction Drug Products

CONSUMER SAFETY OFFICER REVIEW

Application Number: 19-813/SLR-033

Name of Drug: Duragesic (fentanyl transdermal system)

Sponsor: ALZA Corporation

RPM: Judit Milstein

Material Reviewed

N 19-813/SLR-033, dated January 12, 2001, received January 16, 2000, provides for revisions to the 25µg/h, 50 µg/h, 75 µg/h and 100 µg/h Duragesic (fentanyl transdermal system) (b) (4) pouch stock.

Background and Summary Description:

For the purposes of this review, N19-813/SLR-033 was compared with the following submissions:

N19-813/SLR-014, approved November 7, 1994, provided for final printed labeling for the front and back of the pouch stock.

N19-813/SLR-025, approved November 1, 2000, provided for revisions to the 25µg/h, 50 µg/h, 75 µg/h and 100 µg/h back of the pouch stock.

N19-813/SCS-022, approved December 7, 1999, provided for the use of a (b) (4) pouch stock for 25µg/h, 50 µg/h, 75 µg/h and 100 µg/h for Duragesic (fentanyl transdermal system) and didn't contain any changes to the labeling of the pouches.

The changes described below apply to the 25µg/h, 50 µg/h, 75 µg/h and 100 µg/h Duragesic (fentanyl transdermal system) (b) (4) pouch stocks.

Status Report

Reviews completed: Judit Milstein 2-1-01
S. Hertz 2-1-01

N. Ya 2-6-01

CSO review

Please note that the sponsor's proposed revisions are indicated by underlined text. The Agency's proposed revisions are bolded.

Review

Back of the pouch

1. The phrase "~~**KEEP OUT OF REACH OF CHILDREN**~~**"** is removed from the back of the pouch and added to the front of the pouch

2. Added the instructions stating " To open, fold along dotted line and tear slit. (DO NOT CUT) on the right side of the PET pouch stock.

Front of the pouch

The phrase "**KEEP OUT OF REACH OF CHILDREN"** is added to the front of the pouch.

Phrase [redacted] (b) (4) is removed.

Phrase [redacted] (b) (4) removed.

Phrase "R_x only" is added.

Updated code numbers.

Recommendation:

Chemistry reviewer raised the issue of deaths occurred while using inappropriately this product, and suggested that the sponsor add appropriate language on the pouch stock to alert the user of the dangers of this drug.

A team meeting was held, and it was recommended to add to the labeling of the pouch stock the 1st paragraph of the black box.

DDMAC indicated that has no objections to incorporating the 1st paragraph of the black box of the PI into the labeling of the pouch stock, through an E-mail message dated May 5, 2001.

The sponsor was informed of the suggested wording on a fax dated July 10, 2001. A few weeks later the sponsor responded that before accepting the proposed labeling they would like to conduct additional label comprehension studies.

Based on the interactions described above, I recommend an AE action for this supplement

Judit Milstein, Regulatory Project Manager, September 13, 2001.

Cathie Schumaker 9-13-01

Sharon Hertz 2-1-01

Naiqi Ya 2-6-01

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

/s/

Judit Milstein
9/25/01 09:17:58 AM
CSO

Cathie Schumaker
9/25/01 10:59:48 AM
CSO

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-813/S033

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

From:	Kaufman, Michael [PRDUS]
To:	Davies, Kathleen;
CC:	
Subject:	NDA 19-813 Duragesic
Date:	Friday, January 25, 2008 3:24:09 PM
Attachments:	Blank Bkgrd.gif SDOC2755.pdf emfinfo.txt

Dear Kathleen:

Attached is the FDA Field Alert Report that was sent to the San Francisco Field Office. This will be a Company initiated recall. ALZA is continuing their investigation and will be preparing the Recall Notification package to be sent to the District Field Office early next week. I will continue to provide you with update information as it becomes available.

Michael H. Kaufman
Director, Regulatory Affairs
Johnson & Johnson
Pharmaceutical Research & Development, L.L.C.
Tel: (908) 704-4756
Fax: (908) 722-5113
Email: mkaufman@prdus.jnj.com

-----Original Message-----
From: Davies, Kathleen [mailto:Kathleen.Davies@fda.hhs.gov]
Sent: Friday, January 25, 2008 11:20 AM
To: Kaufman, Michael [PRDUS]
Subject: Duragesic

Hi Michael,

I received your VM; I am off-site today.

The approval letter is with Dr. Hertz; I notified her of your situation and will get a status update today for you.

Could you provide me some more information regarding the potential recall? Is this company initiated? Why were discussions initiated? I need to provide Dr. Rappaport more information.

Any additional details you could provide would be quite helpful.

Thanks so much,

Kathleen

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

/s/

Kathleen Davies
2/5/2008 01:49:13 PM
CSO

From:	Kaufman, Michael [PRDUS]
To:	Davies, Kathleen;
CC:	
Subject:	NDA 19-813/S-033: Modification to MG
Date:	Tuesday, January 15, 2008 10:15:46 AM
Attachments:	Blank Bkgrd.gif emfinfo.txt

Dear Kathleen:

The FDA proposed modifications to the Medication Guide are acceptable to the Sponsor.

Michael H. Kaufman
Director, Regulatory Affairs
Johnson & Johnson
Pharmaceutical Research & Development, L.L.C.
Tel: (908) 704-4756
Fax: (908) 722-5113
Email: mkaufman@prdus.jnj.com

> -----Original Message-----
> **From:** Davies, Kathleen [mailto:Kathleen.Davies@fda.hhs.gov]
> **Sent:** Monday, January 14, 2008 4:10 PM
> **To:** Kaufman, Michael [PRDUS]
> **Subject:** RE: NDA 19-813 - Modification to MG
>
> Hi Michael,
>
> I have received feedback from the legal team. We cannot alter the

statement and it must read verbatim as stated in the FR notice. They also stated that it must be contained in the "What are the side effects..." section of the medication guide.

We propose that we include this statement in the side effects section of the medication guide and retain your contact information in the "general information" section (see attached).

Please let me know if this will be acceptable to you.

Thanks,
Kathleen

From: Kaufman, Michael [PRDUS] [mailto:MKAUFMAN@PRDUS.JNJ.COM]
Sent: Wednesday, January 09, 2008 5:23 PM
To: Davies, Kathleen
Subject: RE: NDA 19-813 - Modification to MG

Dear Kathleen:

A question can we modify the statement to read:

"Call your doctor for medical advice about side effects. You may report side effects (b)(4) [redacted] to FDA at 1-800-FDA-1088."

Michael H. Kaufman
Director, Regulatory Affairs
Johnson & Johnson
Pharmaceutical Research & Development, L.L.C.
Tel: (908) 704-4756
Fax: (908) 722-5113
Email: mkaufman@prdus.jnj.com

upon the contents of this e-mail is strictly prohibited. If you have received this e-mail transmission in error, please reply to the sender, so that Johnson & Johnson can arrange for proper delivery, and then please delete the message from your inbox. Thank you.

-----Original Message-----
From: Davies, Kathleen [mailto:Kathleen.Davies@fda.hhs.gov]
Sent: Wednesday, January 09, 2008 9:12 AM
To: Kaufman, Michael [PRDUS]
Subject: NDA 19-813 - Modification to MG

Hi Michael,

Please refer to NDA 19-813 for Duragesic. I received an email from OSE this morning, notifying me that Medication Guides must now incorporate the following statement (see attached FR):

"Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088."

Placement of this statement is not specified, but OSE recommends adding it as the last statement in the section "General Information about..."

I have added it to the Medication Guide red-lined for your review; please let me know your thoughts.

Kathleen

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

/s/

Kathleen Davies
2/5/2008 01:48:35 PM
CSO

Davies, Kathleen

From: Davies, Kathleen
Sent: Wednesday, October 31, 2007 1:47 PM
To: 'Kaufman, Michael [PRDUS]'
Subject: NDA 19813/Duragesic labeling - proposed by FDA
Attachments: Annotated Duragesic USPI_FDA proposed_10-31.pdf; NDA19813_ MG proposed by FDA_10-31-07.pdf; N 19-813_FDA proposed pouch and carton changes 10-31-07.pdf; Blank Bkgrd.gif

Hi Michael,

Please refer to supplement (b) (4) for Duragesic. Please find attached the FDA proposed PI, Medication Guide and Carton/Container. I accepted what we feel to be agreed upon language from our teleconference on August 15, 2007 and any new language still pending agreement is red-lined. In addition, since we are still awaiting additional data regarding the patch being reapplied within 72 hours, we made the PI language the same as the 2005 label at this time, stating that a new patch may be reapplied at a different site.

Note, the medication guide has been re-written by OSE to include formatting for current OSE initiatives concerning medication guides and has separated out the Information for Patients section. We are still reviewing the Information for Patients Section but I hope to get that to you in the next few days.

Please review these proposed labels and provide feedback to the Division on your concurrence or proposal for different wording. Since we are attempting to close this supplement ASAP, timely feedback on this review is requested.

If you have any questions, let me know.

Regards,

Kathleen

40 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page.

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

/s/

Kathleen Davies
11/13/2007 02:51:07 PM
CSO

Davies, Kathleen

From: Davies, Kathleen
Sent: Monday, July 30, 2007 1:44 PM
To: 'Kaufman, Michael [PRDUS]'
Subject: RE: NDA 19813 - Duragesic follow up
Importance: High
Attachments: OSE Comments on Duragesic (b) (4) pdf

Hi Michael,

I have scheduled a teleconference for Wednesday, August 1, from 2:30 to 3:00 PM (EST). Please provide a call-in number for this meeting.

Also, I have attached the comments for discussion at the teleconference. The purpose of the time is to ensure understanding and for you to ask any questions regarding any of the comments.

If you have any questions, let me know.

Kathleen

From: Kaufman, Michael [PRDUS] [mailto:MKAUFMAN@PRDUS.JNJ.COM]
Sent: Friday, July 27, 2007 12:57 PM
To: Davies, Kathleen
Subject: RE: NDA 19813 - Duragesic follow up

Dear Kathleen:

I believe my secure email is now operational again. I would appreciate it if you can confirm that you received this email.

I will have the marketing group request 5 copies of the materials from the distributor and will then then provide them to the Agency.

I will let the individual at the Company know that comments are expected imminently and that a teleconference to discuss will be planned. I will check on individuals availability especially since I not sure who may be on summer vacation in the next 1 or so.

Michael H. Kaufman
Director, Regulatory Affairs
Johnson & Johnson
Pharmaceutical Research & Development, L.L.C
Tel: (908) 704-4756
Fax: (908) 722-5113
Email: mkaufman@prdus.jnj.com

-----Original Message-----
From: Davies, Kathleen [mailto:Kathleen.Davies@fda.hhs.gov]
Sent: Friday, July 27, 2007 11:16 AM
To: Kaufman, Michael [PRDUS]
Subject: NDA 19813 - Duragesic follow up

Hi Michael,

I received your voicemail regarding the Patient Information Kit but did not receive a follow-up email. I hope that you got your secure email working with no trouble.

I think 5 copies of the Patient Information Kit would be acceptable for OSE to review.

I also have some follow-up comments from OSE that I will be forwarding to you later today or Monday. Dr. Hertz would like to have a teleconference with you/your team as well to discuss the comments. I will be scheduling that for later next week and will provide updated information once I have everything scheduled.

If you have any questions let me know.

Thanks, have a good weekend,

Kathleen

3 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

---

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

/s/

Kathleen Davies
8/6/2007 02:59:32 PM
CSO

From:	Compton, Kimberly
To:	Kaufman, Michael [PRDUS];
CC:	Davies, Kathleen; "Narayan, Sujatha [ALZUS]";
Subject:	Copy of PI and pouch for Duragesic
Date:	Wednesday, April 18, 2007 5:32:00 PM
Attachments:	N 19-813 (Duragesic) PI final to firm Apr 2007.doc N 19-813 Duragesic PI final to firm Apr 2007.pdf N 19-813 (Duragesic) Pouchstock final with markups Apr 2007.pdf N 19-813 Summ of pouch changes 4-13-07.doc

---

Hi Michael,

I know Alza/J & J has been waiting for quite some time for the Agency to finish updating the Duragesic PI and pouch labeling and we have finally done so. I am attaching a clean WORD version of the PI with all the new changes included and a PDF version of the PI that shows the markups in color so they can be easily seen by your team. I am also attaching a PDF of an example pouch label, and a summary of the pouch changes we suggest (as the PDF markups can be difficult to read).

Our hope is that your group can discuss these, and either accept them or propose alternates and then submit an amendment with these change (b) (4) We can then review all the material at once and update all the pieces at once. Updating the pouch will also allow us to close out the old S-033.

Please let me (or Kathleen) know if you have any questions, etc. about the lblg or our plan to proceed.

Thanks,

Kim

Kimberly Compton

Kimberly Compton, R.Ph.

Regulatory Project Manager

Division of Anesthesia, Analgesia and

Rheumatology Products (HFD-170)

301-796-1191

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

/s/

Kathleen Davies
4/27/2007 02:46:35 PM
CSO

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*:
Mail: OSE, DMETS, (c/o Diane Smith, Project Manager)

FROM: **Division of Anesthesia, Analgesia and Rheumatology Products, WO Rm 3161**
(c/o Kim Compton, Project Manager)

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
10-06-06		19-813/S-033	Labeling (PI and Pouch)	

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Duragesic (fentanyl transdermal system)	HIGH	Opioid analgesic	10-27-06 (or as quickly as possible, please see note below for additional information).

NAME OF FIRM:

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ■ LABELING REVISION: **Container (pouch) and PI labeling review.**
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

COMMENTS/SPECIAL INSTRUCTIONS:

Please review the enclosed PI and proposed pouch labeling (which firm intends to apply to all strengths) from a safety and medication errors perspective.

While S-033 is (technically) open and deals only with the pouch lableing, the Division is taking this opportunity to update the PI and the pouch labeling and has added the changes we would like to request of the firm to the attached versions and requests DMETS input on these changes as well as other suggestions from DMETS to improve the labeling for this product.

Several months ago the firm was emailed a MG that Jeanine Best drafted based on the enclosed PI and former PPI. We can provide that if it would be helpful, but we are not seeking comment on that at this time.

Please keep in mind that the firm wishes to use the same pouch language (varied for dose strength listing of course) for each strength of patch and the patches vary in size based on strength so some of the pouches have very limited room for material.

Please contact the Division with any questions. Medical Officer is Ellen Fields, and Project Manager is Kim Compton.

Due to the increased interest in fentanyl products of all forms, but with Duragesic (and its generics) in particular, this task has been assigned a high priority so the labeling of the product can be improved as quickly as possible.

Please cc all responses in DFS to the medical officer and project manager.
ATTMTS: Division revised PI and pouch labeling.

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one)
Kim Compton/10-6-06	■ MAIL (DFS) ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

31 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

---

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

/s/

Kimberly Compton

10/6/2006 05:26:52 PM

From: Compton, Kimberly
Sent: Wednesday, July 27, 2005 11:08 AM
To: 'MChrist3@PRDUS.JNJ.COM'; 'Gaumer, Kim [ALZUS]'
Cc: Compton, Kimberly
Subject: Proceeding with resolution of S-033 for N 19-813

HI Mary and Kim,

We have come to a consensus on how we would like to handle S-033 pouch labeling. Please read over our plan and let me know if you have any questions, etc.

We would like you to modify all the pouch patches similar to what was requested in our AE letter from Dr. McCormick, to which you originally responded in Feb 2002, but with the following modifications:

1. Change the order and wording of the box text slightly, putting the reason at the bottom and emphasizing that it is NOT for the listed things. It would read as follows:

    - NOT for acute or post-operative pain
    - NOT for mild or intermittent pain responsive to PRN (as needed) or non-opioid medication
    - NOT in doses greater than 25 mcg/h when starting opioid therapy

    Because life-threatening hypoventilation (slow, shallow breathing) may occur.

2. The last bullet (about the greater than 25 mcg) can be left off the 12 mcg/h patch, as well as the reason ("Because life-threatening…"), if including it is precluded by the amount of space available on the small pouch package.

We would like you to send us new mock-up pouch packages with these changes shown as another amendment to S-033, which we can then make into a "complete response" and therefore take an action on and close out the supplement.

Thanks,
Kim

Kimberly Compton
Kimberly Compton, R.Ph.
Regulatory Project Manager
Division of Anesthesia, Analgesia and
Rheumatology Products (HFD-170)

301-827-7432

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

/s/

Kimberly Compton
7/27/05 11:18:06 AM
CSO

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*:			FROM:	
ODS, DDRE HFD-430, Sandra Birdsong, Project Manager PKLN Rm. 15B08			HFD-170, Division of Anesthetic, Critical Care, and Addiction Drug Products, Kim Compton, Project Manager	
DATE 1/17/03	IND NO.	NDA NO. 19-813/S-033	TYPE OF DOCUMENT SLR supplement	DATE OF DOCUMENT February 15, 2002
NAME OF DRUG Duragesic (fentanyl transdermal system)	PRIORITY CONSIDERATION High		CLASSIFICATION OF DRUG Opioid/narcotic	DESIRED COMPLETION DATE As soon as possible (this supplement is already overdue)

NAME OF FIRM: Alza Corporation

REASON FOR REQUEST

I. GENERAL

☐ NEW PROTOCOL	☐ PRE--NDA MEETING	☐ RESPONSE TO DEFICIENCY LETTER
☐ PROGRESS REPORT	☐ END OF PHASE II MEETING	☐ FINAL PRINTED LABELING
☐ NEW CORRESPONDENCE	☐ RESUBMISSION	☐ LABELING REVISION
☐ DRUG ADVERTISING	☐ SAFETY/EFFICACY	☐ ORIGINAL NEW CORRESPONDENCE
☐ ADVERSE REACTION REPORT	☐ PAPER NDA	☐ FORMULATIVE REVIEW
☐ MANUFACTURING CHANGE/ADDITION	☐ CONTROL SUPPLEMENT	■ OTHER *(SPECIFY BELOW)*:
☐ MEETING PLANNED BY		

COMMENTS/SPECIAL INSTRUCTIONS:

Please review the packet for this product from the safety perspective. This product is a topical opioid narcotic agent for chronic pain. The subject of the material is an SLR supplement that proposes to changes to the pouch stock labeling.

The labeling from the submission will be sent via the internal mail system, under separate cover.

If you have any questions, please contact Kim Compton, Regulatory Project Manager, at 301-827-7432.

Please cc: all written responses in DFS to Parinda Jani, Kim Compton and Pamela Hahn. Thank you for your assistance./KC

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one)
Kimberly Compton, HFD-170/1/17/03/ Jani 1-21-03	■ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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

/s/

Kimberly Compton
1/22/03 06:01:43 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 19-813/S-033

CBE-0 SUPPLEMENT

ALZA Corporation
P. O. Box 7210
Mountain View, CA 94039-7210

Attention: Janne Wissel
Senior VP, Operations

Dear Ms. Wissel:

We have received your supplemental drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Duragesic (fentanyl transdermal system)

NDA Number: 19-813

Supplement Number: 033

Date of Supplement: January 12, 2001

Date of Receipt: January 16, 2001

This supplemental application, submitted as a "Supplement - Changes Being Effected" supplement, proposes the following changes:

1. Addition of the bolded statement "**KEEP OUT OF THE REACH OF CHILDREN"** to the front of the (b) (4) pouch stock.

2. Removal of the statement (b) (4) from the front of the (b) (4) pouch stock.

3. Removal of the statement (b) (4) from the front of the (b) (4) pouch stock.

4. Addition of the statement " Rx only" to the front of the (b) (4) pouch stock.

5. Update of the code numbers on the front of the 25 µg/h, 50µg/h, 75 µg/h, and 100 µg/h (b) (4) pouch stocks.

6. Addition of the instructions stating (b) (4)

[redacted] on the right side of the [redacted] Pouch stock.

7. Change of the ALZA Corporation address from "Palo Alto, CA 94304" to " Mountain View, CA 94043" on the back of the [redacted] pouch stock.

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on March 17, 2001 in accordance with 21 CFR 314.101(a).

Please cite the application number listed above at the top of the first page of any communications concerning this application. All communications concerning this supplemental application should be addressed as follows:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anesthetic, Critical Care, and
Addiction Drug Products, HFD-170
Attention: Division Document Room
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, call me at (301) 827-7440.

Sincerely,

{See appended electronic signature page}

Judit Milstein
Regulatory Project Manager
Division of Anesthetic, Critical Care, and
Addiction Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

/s/

Judit Milstein
1/30/01 02:44:13 PM