CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

19-813 / S-018
19-813 / S-019
19-813 / S-020
19-813 / S-021

Trade Name: Duragesic

Generic Name: (fentanyl transdermal system)

Sponsor: Alza Corporation

Approval Date: July 17, 1997

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APPLICATION NUMBER:

19-813 / S-018
19-813 / S-019
19-813 / S-020
19-813 / S-021

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-813 / S-018
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19-813 / S-021

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 19-813/S-018
NDA 19-813/S-019
NDA 19-813/S-020
NDA 19-813/S-021

JUL 17 1997

Alza Corporation
950 Page Mill Road, P.O. Box 10950
Palo Alto, California 94303-0802

Attention: Darlene O'Banion
Regulatory Associate

Dear Ms. O'Banion:

Please refer to your supplemental new drug applications dated December 8, 1994 (S-018), December 1, 1995 (S-019), February 23, 1996 (S-020) and March 26, 1996 (S-021), received December 12, 1994, December 4, 1995, March 4, 1996 and March 28, 1996, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Duragesic (fentanyl transdermal system), 24, 50, 75, or 100 μg/h.

We acknowledge receipt of your submissions dated July 8, 1996; March 17, 1997 and April 23, 1997.

The supplemental applications provide for the following changes:

S-018--a change to the labeled storage condition
S-019--changes to the physician insert
S-020--deleted the "CII" for each system size
S-021--changes to the patient instructions

We have completed the review of these supplemental applications, including the submitted draft labeling and have concluded that adequate information has been presented to demonstrate that the drug products are safe and effective for use as recommended in the draft labeling submitted on December 8, 1994, December 1, 1995, February 23, 1996, March 26, 1996, March 17, 1997 and April 23, 1997. Accordingly, these supplemental applications are approved effective on the date of this letter. As discussed in the teleconference on April 17, 1997, between you and members of this Division that the following revisions will be made:

1. Change the labels on the graph from MAX to Group MAX and from MIN to Group MIN for clarification

2. Move Duragesic Applied (↑) and remove (↓) to a different location

3. Change the sentence from "This conversion recommendation...." to "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."

4. An additional change, which was not discussed during the teleconference, is recommended for clarity. In the Patients Instruction insert, we suggest replacing "...for whom it was ordered by the doctor...." with "...for whom it was prescribed."

These revisions are terms of the supplemental NDA approval.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FINAL PRINTED LABELING" for approved NDAs 19-813/S-018, 19-813/S-019, 19-813/S-020 and 19-813/S-021. Approval of this submission by FDA is not required before the labeling is used.

Should a letter communicating important information about this drug product (i.e., a "Dear Doctor" letter) be issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20852-9787

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact Ken Nolan, Project Manager, at (301) 443-3741.

Sincerely,

Curt Wright MD for

Cynthia McCormick, M.D.
Director
Division of Anesthetic, Critical Care, and
Addiction Drug Products, HFD-170
Office of Drug Evaluation III
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-813 / S-018
19-813 / S-019
19-813 / S-020
19-813 / S-021

APPROVED LABELING

DURAGESIC®
(FENTANYL TRANSDERMAL SYSTEM) CII

Full Prescribing Information

FOR USE IN OPIOID-TOLERANT PATIENTS ONLY

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

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

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

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

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

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

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

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

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

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

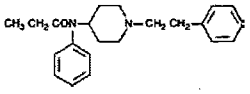
DURAGESIC® can be abused in a manner similar to other opioid agonists, legal or illicit. This risk should be considered when administering, prescribing, or dispensing DURAGESIC® in situations where the healthcare professional is concerned about increased risk of misuse, abuse or diversion.

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

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

DESCRIPTION

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



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

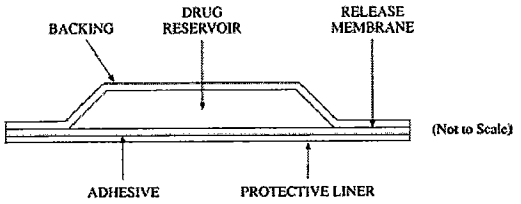
System Components and Structure

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

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

* Nominal delivery rate per hour
** Nominal delivery rate is 12.5 mcg/hr

DURAGESIC® is a rectangular transparent unit comprising a protective liner and four functional layers. Proceeding from the outer surface toward the surface adhering to skin, these layers are:
1) a backing layer of polyester film; 2) a drug reservoir of fentanyl and alcohol USP gelled with hydroxyethyl cellulose; 3) an ethylene-vinyl acetate copolymer membrane that controls the rate of fentanyl delivery to the skin surface; and 4) a fentanyl containing silicone adhesive. Before use, a protective liner covering the adhesive layer is removed and discarded.



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

Do not cut or damage DURAGESIC®. If the DURAGESIC® system is cut or damaged, controlled drug delivery will not be possible, which can lead to the rapid release and absorption of a potentially fatal dose of fentanyl.

CLINICAL PHARMACOLOGY

Pharmacology

Fentanyl is an opioid analgesic. Fentanyl interacts predominately with the opioid mu-receptor. These mu-binding sites are discretely distributed in the human brain, spinal cord, and other tissues. In clinical settings, fentanyl exerts its principal pharmacologic effects on the central nervous system.

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

Opioids increase the tone and decrease the propulsive contractions of the smooth muscle of the gastrointestinal tract. The resultant prolongation in gastrointestinal transit time may be responsible for the constipating effect of fentanyl. Because opioids may increase biliary tract pressure, some patients with biliary colic may experience worsening rather than relief of pain.

While opioids generally increase the tone of urinary tract smooth muscle, the net effect tends to be variable, in some cases producing urinary urgency, in others, difficulty in urination. At therapeutic dosages, fentanyl usually does not exert major effects on the cardiovascular system. However, some patients may exhibit orthostatic hypotension and fainting.

Histamine assays and skin wheal testing in clinical studies indicate that clinically significant histamine release rarely occurs with fentanyl administration. Clinical assays show no clinically significant histamine release in dosages up to 50 mcg/kg.

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

While there is variation in dose delivered among patients, the nominal flux of the systems (12.5, 25, 50, 75, and 100 mcg of fentanyl per hour) is sufficiently accurate as to allow individual titration of dosage for a given patient. The small amount of alcohol which has been incorporated into the system enhances the rate of drug flux through the rate-limiting copolymer membrane and increases the permeability of the skin to fentanyl.

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

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

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

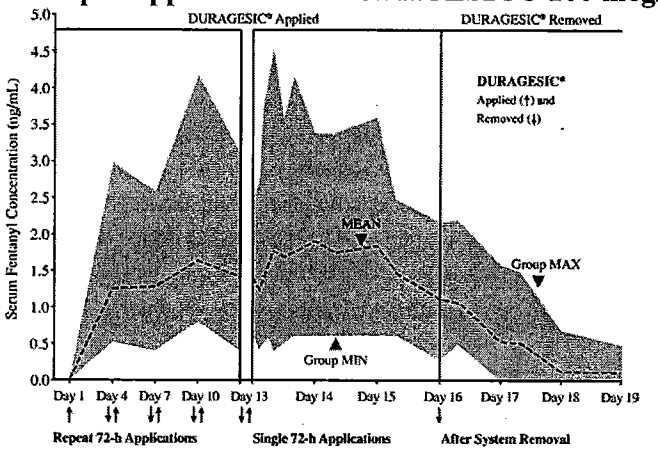


TABLE A
FENTANYL PHARMACOKINETIC PARAMETERS
FOLLOWING FIRST 72-HOUR APPLICATION OF DURAGESIC®

	Mean (SD) Time to Maximal Concentration Tmax (h)	Mean (SD) Maximal Concentration Cmax (ng/mL)
DURAGESIC® 12 mcg/h	27.5 (9.6)	0.3 (0.2)
DURAGESIC® 25 mcg/h	38.1 (18.0)	0.6 (0.3)
DURAGESIC® 50 mcg/h	34.8 (15.4)	1.4 (0.5)
DURAGESIC® 75 mcg/h	33.5 (14.5)	1.7 (0.7)
DURAGESIC® 100 mcg/h	36.8 (15.7)	2.5 (1.2)

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

TABLE B
RANGE OF PHARMACOKINETIC PARAMETERS OF INTRAVENOUS FENTANYL IN PATIENTS

	Clearance (L/h) Range [70 kg]	Volume of Distribution VSS (L/kg) Range	Half-Life t1/2 (h) Range
Surgical Patients	27 - 75	3 - 8	3 - 12
Hepatically Impaired Patients	3 - 80+	0.8 - 8+	4 - 12+
Renally Impaired Patients	30 - 78	–	–

+Estimated

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

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

In 1.5 to 5 year old, non-opioid-tolerant pediatric patients, the fentanyl plasma concentrations were approximately twice as high as that of adult patients. In older pediatric patients, the pharmacokinetic parameters were similar to that of adults. However, these findings have been taken into consideration in determining the dosing recommendations for opioid-tolerant pediatric patients (2 years of age and older). For pediatric dosing information, refer to DOSAGE AND ADMINISTRATION section.

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

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

Skin does not appear to metabolize fentanyl delivered transdermally. This was determined in a human keratinocyte cell assay and in clinical studies in which 92% of the

dose delivered from the system was accounted for as unchanged fentanyl that appeared in the systemic circulation.

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

PHARMACODYNAMICS

Ventilatory Effects
Because of the risk for serious or life-threatening hypoventilation, DURAGESIC® is CONTRAINDICATED in the treatment of post-operative and acute pain and in patients who are not opioid-tolerant. In clinical trials of 357 patients with acute pain treated with DURAGESIC®, 13 patients experienced hypoventilation. Hypoventilation was manifested by respiratory rates of less than 8 breaths/minute or a pCO_2 greater than 55 mm Hg. In these studies, the incidence of hypoventilation was higher in nontolerant women (10) than in men (3) and in patients weighing less than 63 kg (9 of 13). Although patients with impaired respiration were not common in the trials, they had higher rates of hypoventilation. In addition, post-marketing reports have been received that describe opioid-naive post-operative patients who have experienced clinically significant hypoventilation and death with DURAGESIC®.

While most adult and pediatric patients using DURAGESIC® chronically develop tolerance to fentanyl induced hypoventilation, episodes of slowed respirations may occur at any time during therapy. Hypoventilation can occur throughout the therapeutic range of fentanyl serum concentrations, especially for patients who have an underlying pulmonary condition or who receive usual doses of opioids or other CNS drugs associated with hypoventilation in addition to DURAGESIC®. The use of DURAGESIC® is contraindicated in patients who are not tolerant to opioid therapy. The use of DURAGESIC® should be monitored by clinical evaluation, especially within the initial 24-72 hours when serum concentrations from the initial patch will peak, and following increases in dosage. DURAGESIC® should be administered to children only if they are opioid-tolerant and 2 years of age or older.

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

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

CNS Effects
Central nervous system effects increase with increasing serum fentanyl concentrations.

INDICATIONS AND USAGE

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

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

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

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

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

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

CONTRAINDICATIONS

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

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

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

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

WARNINGS

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

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

DURAGESIC® is ONLY for use in patients who are already tolerant to opioid therapy of comparable potency. Use in non-opioid tolerant patients may lead to fatal respiratory depression. Overestimating the DURAGESIC® dose when converting patients from another opioid medication can result in fatal overdose with the first dose. The mean elimination half-life of DURAGESIC® is 17 hours. Therefore, patients who have experienced serious adverse events, including overdose, will require monitoring for at least 24 hours after DURAGESIC® removal since serum fentanyl concentrations decline gradually and reach an approximate 50% reduction in serum concentrations 17 hours after system removal.

DURAGESIC® should be prescribed only by persons knowledgeable in the continuous administration of potent opioids, in the management of patients receiving potent opioids for treatment of pain, and in the detection and management of hypoventilation including the use of opioid antagonists.

All patients and their caregivers should be advised to avoid exposing the DURAGESIC® application site to direct external heat sources, such as heating pads or electric blankets, heat lamps, saunas, hot tubs, and heated water beds, etc., while wearing the system. There is a potential for temperature-dependent increases in fentanyl released from the system resulting in possible overdose and death (see PRECAUTIONS - Patients with Fever/External Heat).

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

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

Misuse, Abuse and Diversion of Opioids

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

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

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

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

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

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

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

The use of concomitant CNS active drugs requires special patient care and observation.

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

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

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

Chronic Pulmonary Disease
Because potent opioids can cause serious or life-threatening hypoventilation, DURAGESIC® should be administered with caution to patients with pre-existing medical conditions predisposing them to hypoventilation. In such patients, normal analgesic doses of opioids may further decrease respiratory drive to the point of respiratory failure.

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

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

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

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

PRECAUTIONS

General

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

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

Cardiac Disease

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

Hepatic or Renal Disease

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

Patients with Fever/External Heat

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

All patients and their caregivers should be advised to avoid exposing the DURAGESIC® application site to direct external heat sources, such as heating pads or electric blankets, heat lamps, saunas, hot tubs, and heated water beds, etc., while wearing the system. There is a potential for temperature-dependent increases in fentanyl release from the system.

Use in Pancreatic/Biliary Tract Disease

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

Tolerance

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

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

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

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

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

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

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

- Do not use soaps, oils, lotions, alcohol, or any other agents that might irritate the skin or alter its characteristics.
- Allow the skin to dry completely prior to patch application.

4. Patients should be advised that DURAGESIC® should be applied immediately upon removal from the sealed package and after removal of the protective liner. Additionally the patient should be advised of the following:
    - The DURAGESIC® patch should not be used if the seal is broken, or if it is altered, cut, or damaged in any way prior to application. This could lead to the rapid release of the contents of the DURAGESIC® patch and absorption of a potentially fatal dose of fentanyl. The transdermal patch should be pressed firmly in place with the palm of the hand for 30 seconds, making sure the contact is complete, especially around the edges.
    - The patch should not be folded so that only part of the patch is exposed.
5. Patients should be advised that while wearing the patch, they should avoid exposing the DURAGESIC® application site to direct external heat sources, such as:
    - heating pads,
    - electric blankets,
    - heat lamps,
    - saunas,
    - hot tubs, and
    - heated water beds, etc.,
6. Patients should be advised that there is a potential for temperature-dependent increase in fentanyl release from the patch that could result in an overdose of fentanyl; therefore, if patients develop a high fever while wearing the patch they should contact their physician.
7. Patients should be advised to fold (so that the adhesive side adheres to itself) and immediately flush down the toilet used DURAGESIC® patches after removal from the skin.
8. Patients should be instructed that, if the gel from the drug reservoir accidentally contacts the skin, the area should be washed clean with clear water and not soap, alcohol, or other chemicals, because these products may increase the ability of fentanyl to go through the skin.
9. Patients should be advised that the dose of DURAGESIC® should NEVER be adjusted without the prescribing health care professional's instruction.
10. Patients should be advised that DURAGESIC® may impair mental and/or physical ability required for the performance of potentially hazardous tasks (e.g., driving, operating machinery).
11. Patients should be advised to refrain from any potentially dangerous activity when starting on DURAGESIC® or when their dose is being adjusted, until it is established that they have not been adversely affected.

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

Drug Interactions

Agents Affecting Cytochrome P450 3A4 Isoenzyme System

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

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

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

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

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

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

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

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

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

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

There are no adequate and well-controlled studies in pregnant women. DURAGESIC® should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

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

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

Labor and Delivery
Fentanyl readily passes across the placenta to the fetus; therefore, DURAGESIC® is not recommended for analgesia during labor and delivery.

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

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

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

DURAGESIC® should be administered to children only if they are opioid-tolerant and 2 years of age or older (see DOSAGE AND ADMINISTRATION and BOX WARNING).

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

Geriatric Use
Information from a pilot study of the pharmacokinetics of IV fentanyl in geriatric patients (N=4) indicates that the clearance of fentanyl may be greatly decreased in the population above the age of 60. The relevance of these findings to DURAGESIC® (fentanyl transdermal system) is unknown at this time.

Since elderly, cachectic, or debilitated patients may have altered pharmacokinetics due to poor fat stores, muscle wasting, or altered clearance, they should not be started on DURAGESIC® doses higher than 25 mcg/h unless they are already tolerating an around-the-clock opioid at a dose and potency comparable to DURAGESIC®-25 (see DOSAGE AND ADMINISTRATION).

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

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

Pre-Marketing Clinical Trial Experience
Although DURAGESIC® use in post-operative or acute pain and in patients who are not opioid-tolerant is CONTRAINDICATED, the safety of DURAGESIC® was originally evaluated in 357 post-operative adult patients for 1 to 3 days and 153 cancer patients for a total of 510 patients. The duration of DURAGESIC® use varied in cancer patients; 56% of patients used DURAGESIC® for over 30 days, 28% continued treatment for more than 4 months, and 10% used DURAGESIC® for more than 1 year.

Hypoventilation was the most serious adverse reaction observed in 13 (4%) post-operative patients and in 3 (2%) of the cancer patients. Hypotension and hypertension were observed in 11 (3%) and 4 (1%) of the opioid-naive patients.

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

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

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

There was no apparent pediatric-specific risk associated with DURAGESIC® use in children as young as 2 years old when used as directed. The most common adverse events were fever (35%), vomiting (33%), and nausea (24%).

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

TABLE 1: ADVERSE EVENTS (at rate of ≥ 1%)
Adult (N=380) and Pediatric (N=291) Clinical Trial Experience

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

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

The following adverse effects have been reported in less than 1% of the 510 adult post-operative and cancer patients studied:
Cardiovascular: bradycardia
Digestive: abdominal distention
Nervous: aphasia, hypertonia, vertigo, stupor, hypotonia, depersonalization, hostility
Respiratory: stertorous breathing, asthma, respiratory disorder
Skin and Appendages, General: exfoliative dermatitis, pustules
Special Senses: amblyopia
Urogenital: bladder pain, oliguria, urinary frequency

Post-Marketing Experience - Adults
The following adverse reactions have been reported in association with the use of DURAGESIC® and not reported in the pre-marketing adverse reactions section above:
Body as a Whole: edema
Cardiovascular: tachycardia
Metabolic and Nutritional: weight loss
Special Senses: blurred vision
Urogenital: decreased libido, anorgasmia, ejaculatory difficulty

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

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

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

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

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

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

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

OVERDOSAGE

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

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

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

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

DOSAGE AND ADMINISTRATION

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

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

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

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

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

General Principles

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

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

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

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

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

(See CONTRAINDICATIONS for further information.)

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

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

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

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

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

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

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

from the drug reservoir accidentally contacts the skin of the patient or caregiver, the skin should be washed with copious amounts of water. Do not use soap, alcohol, or other solvents to remove the gel because they may enhance the drug's ability to penetrate the skin.

Each DURAGESIC® may be worn continuously for 72 hours. The next patch should be applied to a different skin site after removal of the previous transdermal system.

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

Dose Selection

Doses must be individualized based upon the status of each patient and should be assessed at regular intervals after DURAGESIC® application. Reduced doses of DURAGESIC® are suggested for the elderly and other groups discussed in precautions.

DURAGESIC® is ONLY for use in patients who are already tolerant to opioid therapy of comparable potency. Use in non-opioid tolerant patients may lead to fatal respiratory depression.

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

In selecting an initial DURAGESIC® dose, attention should be given to 1) the daily dose, potency, and characteristics of the opioid the patient has been taking previously (e.g., whether it is a pure agonist or mixed agonist-antagonist), 2) the reliability of the relative potency estimates used to calculate the DURAGESIC® dose needed (potency estimates may vary with the route of administration), 3) the degree of opioid tolerance and 4) the general condition and medical status of the patient. Each patient should be maintained at the lowest dose providing acceptable pain control.

Initial DURAGESIC® Dose Selection

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

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

There has been no systematic evaluation of DURAGESIC® as an initial opioid analgesic in the management of chronic pain, since most patients in the clinical trials were converted to DURAGESIC® from other narcotics. The efficacy of DURAGESIC® 12 mcg/h as an initiating dose has not been determined. In addition, patients who are not opioid-tolerant have experienced hypoventilation and death during use of DURAGESIC®. Therefore, DURAGESIC® should be used only in patients who are opioid-tolerant.

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

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

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

TABLE C[1]
DOSE CONVERSION GUIDELINES

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

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

[1]Table C should not be used to convert from DURAGESIC® to other therapies because this conversion to DURAGESIC® is conservative. Use of table C for conversion to other analgesic therapies can overestimate the dose of the new agent. Overdosage of the new analgesic agent is possible (see dosage and administration - discontinuation of DURAGESIC®).

TABLE D[a]
EQUIANALGESIC POTENCY CONVERSION

Name	Equianalgesic Dose (mg) IMb,c	PO
Morphine	10	60 (30)d
Hydromorphone (Dilaudid®)	1.5	7.5
Methadone (Dolophine®)	10	20
Oxycodone	15	30
Levorphanol (Levo-Dromoran®)	2	4

Oxymorphone (Numorphan®)	1	10 (PR)
Meperidine (Demerol®)	75	—
Codeine	130	200

[1]Table D should not be used to convert from DURAGESIC® to other therapies because this conversion to DURAGESIC® is conservative. Use of table D for conversion to other analgesic therapies can overestimate the dose of the new agent. Overdosage of the new analgesic agent is possible (see dosage and administration - discontinuation of DURAGESIC®).

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

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

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

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

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

Oral 24-hour Morphine (mg/day)	DURAGESIC® Dose (mcg/h)
60-134[2]	25
135-224	50
225-314	75
315-404	100
405-494	125
495-584	150

585-674	175
675-764	200
765-854	225
855-944	250
945-1034	275
1035-1124	300

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

[1]Table E should not be used to convert from DURAGESIC® to other therapies because this conversion to DURAGESIC® is conservative. Use of table E for conversion to other analgesic therapies can overestimate the dose of the new agent. Overdosage of the new analgesic agent is possible (see dosage and administration - discontinuation of DURAGESIC®).

[2]Pediatric patients initiating therapy on a 25 mcg/h DURAGESIC® system should be opioid-tolerant and receiving at least 60 mg oral morphine equivalents per day.

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

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

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

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

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

Appropriate dosage increments should be based on the daily dose of supplementary opioids, using the ratio of 45 mg/24 hours of oral morphine to a 12.5 mcg/h increase in DURAGESIC® dose. DURAGESIC®-12 delivers 12.5 mcg/h of fentanyl.

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

Tables C, D, and E should not be used to convert from DURAGESIC® to other therapies. Because the conversion to DURAGESIC® is conservative, use of tables C, D, and E for conversion to other analgesic therapies can overestimate the dose of the new agent. Overdosage of the new analgesic agent is possible.

HOW SUPPLIED

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

DURAGESIC® Dose (mcg/h)	System Size (cm2)	Fentanyl Content (mg)	NDC Number
DURAGESIC®-12	5	1.25	50458-037-05
DURAGESIC®-25	10	2.5	50458-033-05
DURAGESIC®-50	20	5	50458-034-05
DURAGESIC®-75	30	7.5	50458-035-05
DURAGESIC®-100	40	10	50458-036-05

Safety and Handling
DURAGESIC® is supplied in sealed transdermal systems which pose little risk of exposure to health care workers. If the gel from the drug reservoir accidentally contacts

the skin, the area should be washed with copious amounts of water. Do not use soap, alcohol, or other solvents to remove the gel because they may enhance the drug's ability to penetrate the skin. Do not cut or damage DURAGESIC®. If the DURAGESIC® system is cut or damaged, controlled drug delivery will not be possible, which can lead to the rapid release and absorption of a potentially fatal dose of fentanyl.

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

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

Rx only

A schedule CII narcotic. DEA order form required.

Manufactured by:
ALZA Corporation
Mountain View, CA 94043

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

Patient Information

DURAGESIC®
(FENTANYL TRANSDERMAL SYSTEM) CII

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

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

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

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

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

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

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

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

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

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

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

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

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

What is DURAGESIC®?

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

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

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

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

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

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

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

Who should not use DURAGESIC®?

Do not use DURAGESIC®:

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

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

Tell your health care provider about all of your medical problems, especially if you have:

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

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

Tell your health care provider if you:

- **Are pregnant or planning to become pregnant.** DURAGESIC® may harm your unborn baby.
- **Are breast feeding.** The medicine in DURAGESIC® passes into your milk and can harm your baby.

Some medicines may cause serious or life-threatening side effects when used with DURAGESIC®. Tell your health care provider about all the medicines you take including prescription and non-prescription medicines, vitamins, and herbal supplements. Sometimes, the doses of certain medicines and DURAGESIC® need to be changed when used together. Be especially careful about other medicines that make you sleepy such as other pain medicines, sleeping pills, anxiety medicines, antihistamines, or tranquilizers.

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

What should I know about using DURAGESIC® in children?

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

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

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

How do I use DURAGESIC®?

- Follow your health care provider's directions exactly. Your health care provider may change your dose after seeing how the medicine affects you.
- **Do not use the DURAGESIC® patch if the seal is broken or the patch is cut, damaged or changed in any way. Using a patch that is cut, damaged, or changed in any way can expose you to the contents of the patch, which contains a potentially fatal dose of medicine.**
- Do not change your dose or stop using DURAGESIC® unless your health care provider tells you to. Do not use DURAGESIC® more often than prescribed. (See the end of this leaflet for "How and when to apply DURAGESIC®.")
- Do not wear more than <u>one</u> DURAGESIC® patch at a time, unless your health care provider tells you to do so.
- Call your health care provider right away if you get a fever higher than 102°F. A fever may cause too much of the medicine in DURAGESIC® to pass into your body. Your health care provider may tell you to use a lower dose while you have a fever.
- If you use more DURAGESIC® than your health care provider has prescribed or overdose, get emergency medical help right away.
- If you have concerns about abuse or addiction when using your pain medicine or if you have experienced drug or alcohol abuse or addiction in the past, or have a family history of these problems, talk to your health care provider.
- After you have stopped using a patch, be sure to fold the sticky sides of the patch together and flush it down the toilet. Do not put used DURAGESIC® patches in a garbage can.
- If your health care provider tells you to stop using DURAGESIC®, throw away the unused packages. Open the unused packages and fold the sticky sides

of the patches together, and flush them down the toilet. (See "What should I avoid while using DURAGESIC®")

What should I avoid while using DURAGESIC®?

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

- **Do not drink any alcohol while using DURAGESIC®.** It can increase your chances of having dangerous side effects.

- **Do not drive, operate heavy machinery, or do other possibly dangerous activities** until you know how DURAGESIC® affects you. DURAGESIC® can make you sleepy. Ask your health care provider to tell you when it is okay to do these activities.

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

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

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

What are the possible side effects of DURAGESIC®?

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

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

- Have trouble breathing
- Have extreme drowsiness with slowed breathing

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

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

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

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

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

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

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

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

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

How and where to apply DURAGESIC®

In the hospital, your health care provider or other medical person will apply DURAGESIC® for you. At home, you or a member of your family may apply DURAGESIC® to your skin. You need to check the patches often to make sure that they are sticking well to the skin. In young children and people who have impaired thinking, put the patch on the upper back. This will lower the chances that the patch will be removed

1. **Prepare:** For adults, put the patch on the chest, back, flank (sides of the waist), or upper arm in a place where there is no hair. Put it on right away after you have removed it from the pouch and after you have removed the protective liner. Avoid sensitive areas or those that move around a lot. If there is hair, **do not shave (shaving irritates the skin)**. Instead, clip hair as close to the skin as possible. Clean the skin area with clear water **only**. **Pat skin completely dry.** Do not use anything on the skin (soaps, lotions, oils, alcohol, etc.) before the patch is applied.

Graphic of man clipping chest hair with scissors

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

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

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

Graphic of man pressing patch with palm of hand

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

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

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

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

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

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

When to apply DURAGESIC®

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

Water and DURAGESIC®

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

Disposing of DURAGESIC®

- Before putting on a new DURAGESIC® patch, remove the patch you have been wearing.

- Fold the used DURAGESIC® patch in half so that the sticky side sticks to itself. **Flush the used DURAGESIC® down the toilet right away. A used DURAGESIC® patch may be dangerous for or even lead to death in babies, children, pets, and adults who have not been prescribed DURAGESIC®.**

- Throw away any DURAGESIC® patches that are left over from your prescription as soon as they are no longer needed. Remove the leftover patches from their protective pouch and remove the protective liner. **Fold the patches in half with the sticky sides together, and flush the patches down the toilet.** Do not flush the pouch or the protective liner down the toilet. These items can be thrown away in a garbage can.

Safety and handling of DURAGESIC®

DURAGESIC® is a patch with a drug-containing gel sealed inside. This design keeps the gel from getting on your hands or body. If the gel from the drug reservoir accidentally contacts the skin, the area should be washed with large amounts of water. Do not use soap, alcohol, or other solvents to remove the gel because they may increase the drug's ability to go through the skin.

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

The patch must be used only on the skin of the person for whom it was prescribed. If the patch comes off and accidentally sticks to the skin of another person, take the patch off of that person right away, wash the area with water, and seek immediate medical attention. Call a health care provider or poison control center.

Prevent theft and misuse. DURAGESIC® contains an opioid narcotic pain medicine that can be a target for people who abuse prescription medicines. Keep your DURAGESIC® in a safe place, to protect it from theft. Never give DURAGESIC® to anyone else because it may be dangerous to them. Selling or giving away this medicine is against the law.

How should DURAGESIC® be stored?

Store DURAGESIC® below 77° F (25° C). Remember, the inside of your car can reach temperatures much higher than this in the summer.

Keep DURAGESIC® in its protective pouch until you are ready to use it.

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

General information about the safe and effective use of DURAGESIC®

Medicines are sometimes prescribed for conditions that are not mentioned in patient information leaflets. Do not use DURAGESIC® for a condition for which it was not prescribed. Do not give DURAGESIC® to other people, even if they have the same symptoms you have. **DURAGESIC® can harm other people and even cause death. Sharing DURAGESIC® is against the law.**

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

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

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

For questions about DURAGESIC® call the JANSSEN Customer Action Center at 1-800-JANSSEN (1-800-526-7736) 9A.M. to 5 P.M. EST, Monday through Friday.

This patient information has been approved by the United States Food and Drug Administration.

What are the ingredients of DURAGESIC®?

Active Ingredient: fentanyl

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

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

RX ONLY

MANUFACTURED BY:
ALZA CORPORATION
MOUNTAIN VIEW, CA 94043

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

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-813 / S-018
19-813 / S-019
19-813 / S-020
19-813 / S-021

MEDICAL REVIEW

Medical Officer Review

NDA: Transdermal Fentanyl
Submission Serial # NDA 19-813.019
Sponsor: JannssenALZA
Drug: Duragesic
Type of Submission: LABELING AMENDMENT
Proposed Indication: Analgesia
Medical Officer: C. Wright
Peer Medical Officer: C Winchell
PK Reviewer: S. Dodapaneini
Letter Date from Sponsor: 12/1/95
Date Received by CDER: 12/4/95
Date Received by Reviewer: 2/11/97
Review Date: 2/11/97
CSO: M. Wright

General Information (Key Words) Duragesic, Labeling, Overdose, PK, Dosage, Conversion Ratio
Pharmacological Category: Narcotic analgesic
Route of Administration: Transdermal
Study Title: N/A
Principal Investigator: N/A
Protocol #: N/A
Study Location: N/A
Other Study Drugs: N/A

Background: The sponsor wishes to alter the labeling to improve its clarity and accuracy.

Specific Changes Requested (please refer to marked up copy called "Redline/Strikeout" copy in jacket SLR-019).

The sponsor wants purely grammatical or expository changes repositioning material already in the label that do not alter meaning on pages 4, 14, 15, 21, & 24. These are unobjectionable.

On pages 5, 6 & 7 the sponsor wishes to alter the tables and graphs describing Duragesic pharmacokinetics to improve clarity. The proposed changes may need some alteration to avoid a spurious inference about individual patient blood level trajectories, (please see the PK review) but the effect is to improve clarity and is acceptable.

[ ]

On page 22, the sponsor has re-ordered the references. I have no objection.

On pages 23, 24 & 25 the sponsor describes the dosage tables converting TO Duragesic as "conservative" and warns against their usage in converting back FROM Duragesic. This change is an improvement, but may require further work (see below).

Discussion: All of the changes (excluding minor changes in the graphic) are acceptable, but I am concerned that the word "conservative" may be ambiguous in this usage. It might be better to actually describe the actual effect, such as

"[ ]

In addition, consideration might be given to inclusion of a table to convert a patient FROM Duragesic TO another opioid.

Medical Officer's Conclusion: Labeling changes acceptable with minor modification to graphic as recommended by PK. Optional suggestions on further improvement will be conveyed to sponsor in planned TELECON.

Curtis Wright, Medical Reviewer _____

Peer Reviewer_____

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CLINICAL PHARMACOLOGY/ BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA: 19-813	**SUPPLEMENT NO.**: 019
NAME: Duragesic® (fentanyl transdermal system)	
SPONSOR: Alza Corporation, 950 Page Mill Road, P.O.Box, Palo Alto, CA	
SUBMISSION TYPE: Labeling Supplement	
SUBMISSION DATE: December 1, 1995	
REVIEWER: Suresh Doddapaneni, Ph.D.	**REVIEW DATE:** May 13, 1997

SYNOPSIS

Alza Corporation submitted this supplement for Duragesic® (fentanyl transdermal system) to revise the physician insert to improve its clarity and accuracy. Regarding the pharmacokinetic section, changes were made to maintain consistency in units, provide clarity in statements, and provide clarification of the data presented in tables and graphs. Essentially, the existing information was rearranged. All the suggested changes were reasonable and acceptable except for the graph on page 6 where ***text and indicators for the mean, maximum, and minimum*** serum concentration-time profiles were added. The text should say mean, group maximum, and group minimum so as not to mistake the maximum and/or minimum profile pertaining to a single individual. This proposal was accepted by the sponsor.

Suresh 5/14/97

Suresh Doddapaneni, Ph.D.
Pharmacokineticist
DPE II/OCPB

CC:
NDA 19-813 (Original), HFD-170 (Division files, Mwright), HFD-870 (Doddapaneni)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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19-813 / S-020
19-813 / S-021

ADMINISTRATIVE DOCUMENTS AND CORRESPONDENCE

Labeling Review

NDA 19-813/S-018,S-019,S-020,S-021

Drug: Duragesic™ (fentanyl transdermal system)

Sponsor: Alza Corporation

Date:

S-018 Letter Date: December 8, 1994
CDER Date: December 12, 1994
Review Date: May 9, 1997

S-019 Letter Date: December 1, 1995
CDER Date: December 4, 1995
Review Date: May 9, 1997

S-20 Letter Date: February 23, 1996
CDER Date: March 4, 1996
Review Date: May 9, 1997

Amendment to S-019 Letter Date: March 17, 1997
CDER Date: March 18, 1997
Review Date: May 9, 1997

S-021 Letter Date: March 26, 1996
CDER Date: March 28, 1996
Review Date: May 9, 1996

Supplemental New Correspondence to S-020 Letter Date: July 8, 1996
CDER Date: July 10, 1996
Review Date: May 9, 1997

Amendment to S-019,S-020, & S-021 Letter Date: April 23, 1997
CDER Date: April 25, 1997
Review Date: May 9, 1997

Type of Submissions: Supplemental Label Revision (SLR)-018
Supplemental Label Revision (SLR)-019
Supplemental Label Revision (SLR)-020
Supplemental New Correspondence (SNC) to SLR-020
Minor Labeling Amendment (BB) to SLR-019
Supplemental Label Revision (SLR)-021
Major Labeling Amendment (BL) to SLR-019, SLR-020, & SLR-021

Material Reviewed: The above submissions were compared to the last approved labeling contained in SLR-017.

Discussion:

SLR-018 submitted December 8, 1994 provided for a change to the labeled storage condition for Duragesic systems. SLR-019, submitted December 1, 1995, provided for changes to the Physician Insert and included three final toxicology reports to support changes made to the *Carcinogenesis, Mutagenesis and Impairment of Fertility* section of the labeling. BB to SLR-019, submitted March 18, 1997, provided a response to our March 13, 1997 fax (See Attachment 1). SLR-020, submitted February 23, 1996, provided for changes to the Systems Print. SNC to SLR-020, submitted July 8, 1996, provided samples showing the proposed print. SLR-021, submitted March 26, 1996, provided for changes to the Patients Instructions. The BL to SLR-019, SLR-020, and SLR-021, submitted April 23, 1997, provided a Summary of the labeling changes that were agreed on during the April 17, 1997 teleconference (See Attachment 2). The proposed changes submitted in the above mentioned submissions were reviewed by Dr. Curtis Wright, Medical Officer, Dr. Robert Bedford, Medical Officer, Dr. Suresh Doddapaneni, Pharmacokineticts, Dr. Lucy Jean, Pharmacologist, Juanita Ross, MS, Chemist, Dr. Michael Klein, Controlled Substance Drug Products, and Millie Wright, Project Manager. The results of the reviews are detailed below.

SLR-018

SLR-018 provided for a change to the labeled storage condition for Duragesic systems. Previously the statement read " _____ ' to **"Do not store...above 77°F (25°C).** The revision was made to the physician package insert, the patient instructions for use, the cartons, and the back of the immediate containers (pouches). Ms. Juanita Ross, Chemist, reviewed the changes and noted her agreement with the Sponsor's changes in a memo dated March 12, 1997

SLR-019

SLR-019 provided for changes to the physician insert for Durageisic systems. Attachment 4 lists the changes made by the Sponsor and their rationale. SLR-019 was reviewed by Dr. Curtis Wright and Dr. Suresh Doddapneni (See Attachments 5 & 6) My comparison of the labeling contained in SLR-019 to the last approved labeling (approved November 7, 1994) in SLR-017, revealed no other changes than those identified by the Sponsor. Dr. Wright found the labeling changes acceptable, but had suggestions for improvement and Dr. Doddapaneni requested minor modification to graphic. The Sponsor was contacted and a telecon was scheduled for April 17, 1997. A fax dated March 13, 1997 listed the topics for discussion and requested a copy of the data that the Sponsor used to support the changes in the graph. (See Attachment 1) In response to Dr. Doddapaneni's request, a labeling amendment to SLR-019, submitted March 17, 1997, contained the data used by the Sponsor to generate the pharmacokinetic graph located on page 6. The changes made in the Clinical pharmacology section were acceptable to Dr. Jean.

SLR-019 (cont)

During the April 17th telecon, the FDA communicated their recommendations to the Sponsor.(See Attachment 1 & 2) Agreement was reached between the Sponsor and the FDA on the changes that needed to be made to the labeling submitted for SLR-019. The labeling amendment submitted by the Sponsor on April 23, 1997 listed the Sponsor's understanding of the agreements reached on SLR-018, SLR-019, SLR-020, and SLR-021. These changes were as agree upon.

SLR-020

SLR-020 proposed deleting "CII" for each system size. The Sponsor reported the controlled substance symbol (CII) is printed on the system pouch and the commercial carton. It was the Sponsor understanding the CII symbol is not required on the System. They proposed removing the CII from the print mat and use the same print mat for both Canada and the United States. The commercial container will not be changed. Before making a final decision, Dr. Klein requested a sample of the system without the CII symbol. The Sponsor provided samples in their July 8, 1996 submission. After examining the samples, Dr. Klein found their proposed changes to be acceptable.

SLR-021

SLR-021 provided changes to the patients instructions for Duragesisc systems. Attachment 10 lists the proposed changes. Comparison to the patients instructions contained in SLR-021 to the last approved patients instructions contained in SLR-017 (approved November 7, 1994) revealed no other changes. The proposed changes were found to be acceptable, however, Dr. Bedford proposed the following change for clarity.

In the paragraph added, which reads, "The patch must be used only on the skin of the person for whom it was ordered by the doctor. If the patch dislodges and accidently adheres to the skin of another person, take the patch off immediately and call a doctor." Dr. Bedford suggests replacing, "....for whom it was ordered by the doctor." With "for whom it was prescribed."

Other Comments

Review of the labeling revealed no other changes than those identified by the Sponsor

Recommendation

The labeling supplements submitted (SLR-018, SLR-019, SLR-020, and SLR-021) and the amendments (BB to SLR-019 and BL to SLR-019, SLR-020, and SLR-021) should be approved.

Millie Wright 5/21/97

Millie Wright
Project Manager

Corinne P. Moody

Concur: Corinne P. Moody
Chief, Project Management Staff

cc:
Original NDA 19-813/S-018,19,20,&21
HFD-170/Division File
HFD-170/Nolan

ATTACHMENTS (11)

MEMORANDUM OF MEETING MINUTES

Meeting Date: April 17, 1997

Time: 3 P.M.

Location: HFD-170/9B-45, Conf. Room 2

Application: NDA 19-813/SLR-019

Type of Meeting: Telecon

Meeting Chair: Suresh Doddapaneni, Ph.D.

Meeting Recorder: Millie Wright, Project Manager

FDA Attendees, titles, and Office/Division:

Curtis Wright, M.D., M.P.H./Medical Officer
Suresh Doddapaneni, Ph.D/Pharmacokineticist
Millie Wright, Project Manager

External Constituent Attendees and titles:

Alza: Ms. Janne Wissel, Vice President, Regulatory Affairs
Ms. Mirka Dunn, Director of Regulatory Affairs
Ms. Katy Morton, Associate Director of Regulatory Affairs
Ms. Darlene O'Banion, Senior Regulatory Associate
Mr. Sunee Gupta, Senior Director, Clinical Pharmacology
Ms. Mary Southam, Executive Director, Clinical Development.

Janssen: Ms. Melody Eble, Regulatory Associate

Background:

A telecon was scheduled to discuss concerns and suggestions from Drs. Wright and Doddapaneni for the Sponsor's labeling supplement (SLR-019) (See Attached March 13, 1997 fax)

Meeting Objectives:

To reach agreement on the the wording/graphs in the supplement.

Discussion Points (bullet format):

1. Graph on pg. 6, entitled Serum Fentanyl Concentrations Following Multiple Application of Duragesic 100 μg/h
2. Page 21 (Vol 196.1/069), sentence in the section entitled initial Duragesic Dose Selection

Decisions (agreements) reached:

1. Change the labels on the graph from MAX to Group MAX and from MIN to Group MIN for clarification

2. Move Duragesic Applied (↑) and remove (↓) to a different location

3. Change the sentence from "This conversion recommendation...." to "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."

Unresolved issues or issues requiring further discussion:

1.

WITHHOLD 30 PAGE(S)

Draft Labeling

Admin Review

Action Items:

Item	Responsible Person	Due Date
1. Sponsor to submit BL detailing agreed upon changes	Darlene O'Banion	ASAP
2. FDA to finalize SLRs reviews	Millie Wright	ASAP

Minutes Preparer: Millie Wright

Chair Concurrence: D Sarver 5/20/97

Attachments/Handouts:

cc: Original NDA 19-813
HFD-/Div. Files
HFD-170/Nolan

Drafted by: M.Wright

MEETING MINUTES

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

Date March 28, 1996

NDA No. 19-813

ALZA Corporation
950 Page Mill Rd., PO Box 10950
Palo Alto, CA 94303-0802

Attention: Mirka Dunn, Director
Regulatory Affairs

Dear Sir/Madam:

We acknowledge receipt of your supplemental application for the following:

Name of Drug: Duragesic (fentanyl transdermal system)

NDA Number: 19-813

Supplement Number: S-021

Date of Supplement: March 26, 1996

Date of Receipt: March 28, 1996

Unless we find the application not acceptable for filing, this application will be filed under Section 505(b)(1) of the Act on May 27, 1996 in accordance with 21 CFR 314.101(a).

All communications concerning this NDA should be addressed as follows:

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

Sincerely yours,

Corinne P. Moody

Acting Chief, Project Management Staff
Division of Anesthetic, Critical Care and Addiction Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

FORM FDA 3217e (11/95)

★ U.S. GPO: 1995-404-897/20717

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 19-813

December 13, 1994

Alza Corporation
950 Page Mill Road
P.O. Box 10950
Palo Alto, CA 94303-0802

Attention: Elizabeth A. Clark

Dear Ms. Clark

We acknowledge receipt of your supplemental application for the following:

Name of Drug: Duragesic (fentanyl) Transdermal System

NDA Number: 19-813

Supplement Number: S-018

Date of Supplement: December 8, 1994

Date of Receipt: December 12, 1994

Should you have any questions, please contact

Leslie Vaccari
Project Manager
(301) 443-3741

Sincerely yours,

For Project Manager
Pilot Drug Evaluation Staff,
HFD-007
Center for Drug Evaluation and Research