DURAGESIC®
(FENTANYL TRANSDERMAL SYSTEM) CII

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

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

(See CONTRAINDICATIONS for further information.)

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

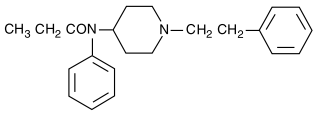
DURAGESIC® is indicated for treatment of chronic pain (such as that of malignancy) that:

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

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

DESCRIPTION

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



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

System Components and Structure

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

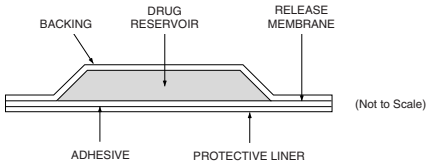
Dose* (µg/h)	Size (cm^2)	Fentanyl Content (mg)
25	10	2.5
50**	20	5
75**	30	7.5
100**	40	10

*Nominal delivery rate per hour

**FOR USE ONLY IN OPIOID-TOLERANT PATIENTS

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

1) a backing layer of polyester film; 2) a drug reservoir of fentanyl and alcohol USP gelled with hydroxyethyl cellulose; 3) an ethylene-vinyl acetate copolymer membrane that controls the rate of fentanyl delivery to the skin surface; and 4) a fentanyl containing silicone adhesive. Before use, a protective liner covering the adhesive layer is removed and discarded.



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

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

CLINICAL PHARMACOLOGY

Pharmacology

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

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

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

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

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

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

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

Pharmacokinetics (see graph and tables)

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

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

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

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

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

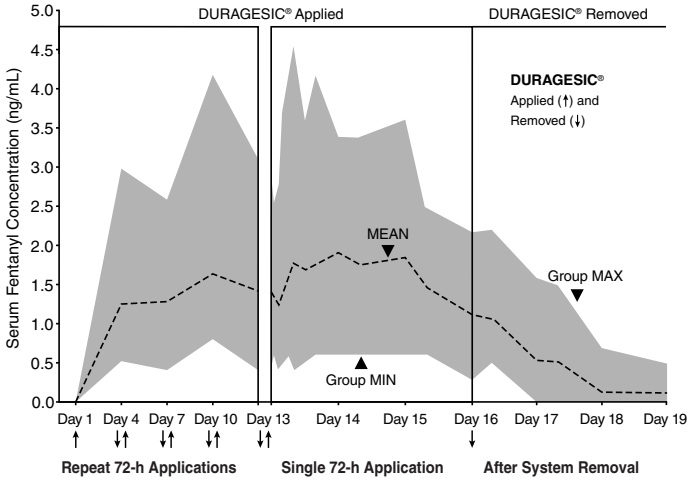


TABLE A
FENTANYL PHARMACOKINETIC PARAMETERS FOLLOWING FIRST 72-HOUR APPLICATION OF DURAGESIC®

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

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

TABLE B
RANGE OF PHARMACOKINETIC PARAMETERS OF INTRAVENOUS FENTANYL IN PATIENTS

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

+ Estimated

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

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

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

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

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

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

Pharmacodynamics

Analgesia

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

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

Ventilatory Effects

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

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

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

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

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

Cardiovascular Effects

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

CNS Effects

In opioid-naive patients, central nervous system effects increase when serum fentanyl concentrations are greater than 3 ng/mL.

CLINICAL TRIALS

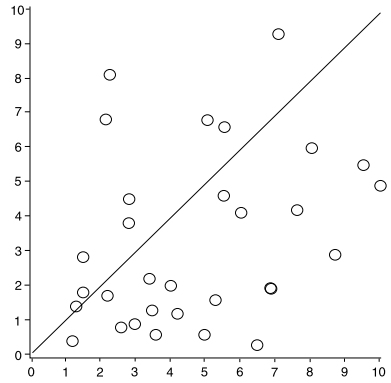
Adults

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

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

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

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



Pediatrics

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

INDICATIONS AND USAGE

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

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

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

CONTRAINDICATIONS

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

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

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

WARNINGS

The safety of DURAGESIC® (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 AGE 2 YEARS OR OLDER **(see PRECAUTIONS-Pediatric Use).**

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

DURAGESIC® SHOULD BE PRESCRIBED ONLY BY PERSONS KNOWLEDGEABLE IN THE CONTINUOUS ADMINISTRATION OF POTENT OPIOIDS, IN THE MANAGEMENT OF PATIENTS RECEIVING POTENT OPIOIDS FOR TREATMENT OF PAIN, AND IN THE DETECTION AND MANAGEMENT OF HYPOVENTILATION INCLUDING THE USE OF OPIOID ANTAGONISTS.

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

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

PRECAUTIONS

General

DURAGESIC® (fentanyl transdermal system) doses greater than 25 µg/h are too high for initiation of therapy in non-opioid-tolerant patients and should not be used to begin DURAGESIC® therapy in these patients. Children converting to DURAGESIC® should be opioid-tolerant (see BOX WARNING).

DURAGESIC® may impair mental and/or physical ability required for the performance of potentially hazardous tasks (e.g., driving, operating machinery). Patients who have been given DURAGESIC® should not drive or operate dangerous machinery unless they are tolerant to the side effects of the drug.

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

Hypoventilation (Respiratory Depression)

Hypoventilation may occur at any time during the use of DURAGESIC®.

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

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

Chronic Pulmonary Disease

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

Head Injuries and Increased Intracranial Pressure

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

Cardiac Disease

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

Hepatic or Renal Disease

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

Patients with Fever/External Heat

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

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

Drug Interactions

Central Nervous System Depressants

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

Agents Affecting Cytochrome P450 3A4 Isoenzyme System

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

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

Drug or Alcohol Dependence

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

Ambulatory Patients

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

Carcinogenesis, Mutagenesis, and Impairment of Fertility

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

Pregnancy — Pregnancy Category C

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

Labor and Delivery

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

Nursing Mothers

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

Pediatric Use

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

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

Geriatric Use

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

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

Information for Patients

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

Disposal of DURAGESIC®

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

If the gel from the drug reservoir accidentally contacts the skin, the area should be washed with clear water.

ADVERSE REACTIONS

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

Pre-Marketing Clinical Trial Experience

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

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

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

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

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

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

The most common adverse events were fever (35%), vomiting (33%), and nausea (24%).
Adverse events reported in pediatric patients at a rate of ≥ 1% are presented in Table 1.

TABLE 1: ADVERSE EVENTS (at rate of ≥ 1%)

Adult (N=153) and Pediatric (N=291) Pre-Marketing Clinical Trial Experience

Body System	Adults	Pediatrics
Body as a Whole	Abdominal pain*, headache*	Pain*, headache*, fever, syncope, abdominal pain, allergic reaction, flushing
Cardiovascular	Arrhythmia, chest pain	Hypertension, tachycardia
Digestive	Nausea**, vomiting**, constipation**, dry mouth**, anorexia*, diarrhea*, dyspepsia*, flatulence	Nausea**, vomiting**, constipation*, dry mouth, diarrhea
Nervous	Somnolence**, confusion**, asthenia**, dizziness*, nervousness*, hallucinations*, anxiety*, depression*, euphoria*, tremor, abnormal coordination, speech disorder, abnormal thinking, abnormal gait, abnormal dreams, agitation, paresthesia, amnesia, syncope, paranoid reaction	Somnolence*, nervousness*, insomnia*, asthenia*, hallucinations, anxiety, depression, convulsions, dizziness, tremor, speech disorder, agitation, stupor, confusion, paranoid reaction
Respiratory	Dyspnea*, hypoventilation*, apnea*, hemoptysis, pharyngitis, hiccups	Dyspnea, respiratory depression, rhinitis, coughing

TABLE 1: ADVERSE EVENTS (at rate of ≥ 1%) (continued)

Adult (N=153) and Pediatric (N=291) Pre-Marketing Clinical Trial Experience

Body System	Adults	Pediatrics
Skin and Appendages	Sweating**, pruritus*, rash, application site reaction – erythema, papules, itching, edema	Pruritus*, application site reaction*, sweating increased, rash, rash erythematous, skin reaction localized
Urogenital	Urinary retention*	Urinary retention

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

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

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

Cardiovascular: bradycardia

Digestive: abdominal distention

Nervous: aphasia, hypertonia, vertigo, stupor, hypotonia, depersonalization, hostility

Respiratory: stertorous breathing, asthma, respiratory disorder

Skin and Appendages, General: exfoliative dermatitis, pustules

Special Senses: amblyopia

Urogenital: bladder pain, oliguria, urinary frequency

Post-Marketing Experience - Adults

The following adverse reactions 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

DRUG ABUSE AND DEPENDENCE

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

OVERDOSAGE

Clinical Presentation

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

Treatment

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

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

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

DOSAGE AND ADMINISTRATION

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

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

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

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

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

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

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

Dose Selection

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

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

In selecting an initial DURAGESIC® dose, attention should be given to 1) the daily dose, potency, and characteristics of the opioid the patient has been taking previously (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, if any, and 4) the general condition and medical status of the patient. Each patient should be maintained at the lowest dose providing acceptable pain control.

Initial DURAGESIC® Dose Selection

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

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

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

Table C[a]
EQUIANALGESIC POTENCY CONVERSION

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

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

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

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

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

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

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

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

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

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

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

Because of the increase in serum fentanyl concentration over the first 24 hours following initial system application, the initial evaluation of the maximum analgesic effect of DURAGESIC® cannot be made before 24 hours of wearing. The initial DURAGESIC® dosage may be increased after 3 days (see 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® dosage may be increased after 3 days based on the daily dose of supplemental analgesics required by the patient in the second or third day of the initial application.

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

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

Discontinuation of DURAGESIC®

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

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

HOW SUPPLIED

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

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

*FOR USE ONLY IN OPIOID-TOLERANT PATIENTS.

Safety and Handling

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

KEEP DURAGESIC® OUT OF THE REACH OF CHILDREN

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

Rx only

DEA order form required. A schedule CII narcotic.

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