LACHMAN CONSULTANT SERVICES, INC.
Westbury, NY 11590

ATTACHMENT 3

[Proposed Labeling for Fentanyl Transdermal System]

FENTANYL TRANSDERMAL SYSTEM (Schedule II symbol)

Full Prescribing Information

BECAUSE SERIOUS OR LIFE-THREATENING HYPOVENTILATION COULD OCCUR, FENTANYL TRANSDERMAL SYSTEM IS CONTRAINDICATED

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

(See CONTRAINDICATIONS for further information.)

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

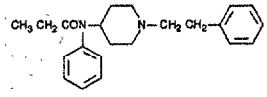
Fentanyl transdermal system is indicated for treatment of chronic pain (such as that of malignancy) that:

- **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 37.5, 50, 62.5, 75, 87.5, and 100 mcg/h dosages should ONLY be used in patients who are already on and are tolerant to opioid therapy.

DESCRIPTION

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 mcg/h per 10 cm^2). The composition per unit area of all system sizes is identical. Each system also contains 0.1 mL of alcohol USP per 10 cm^2.

Dose* (mcg/h)	Size (cm^2)	Fentanyl Content (mg)
25	10	2.5
37.5**	15	3.75
50**	20	5
62.5**	25	6.25
75**	30	7.5
87.5**	35	8.75
100**	40	10

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

[information specific to the drug product will be included when the ANDA is submitted.]

CLINICAL PHARMACOLOGY

Pharmacology

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

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

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

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

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

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

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

Pharmacokinetics (see graph and tables)

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.

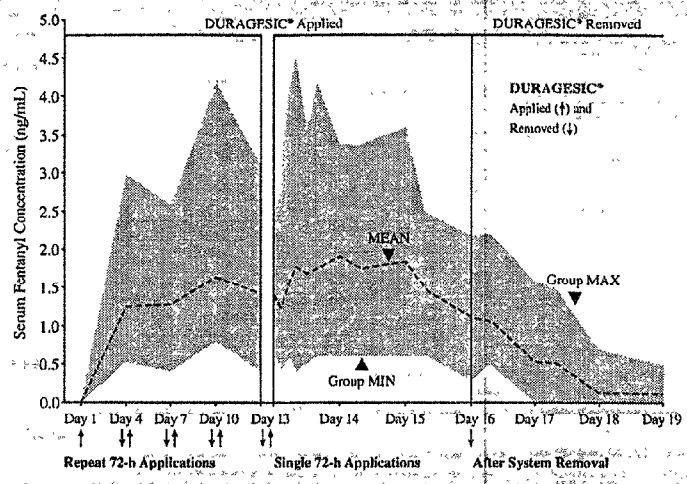
While there is variation in dose delivered among patients, the nominal flux of the systems (25, 50, 75, and 100 μg of fentanyl per hour) is sufficiently accurate as to allow individual titration of dosage for a given patient. The small amount of alcohol which has been incorporated into the system enhances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

Following fentanyl transdermal system 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 fentanyl transdermal system 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 fentanyl transdermal system 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 Fentanyl Transdermal System 100 mcg/h (n=10)



[Replace "DURAGESIC®" in the above figure with "Fentanyl Transdermal System.]

TABLE A

FENTANYL PHARMACOKINETIC PARAMETERS FOLLOWING FIRST 72-HOUR APPLICATION OF FENTANYL TRANSDERMAL SYSTEM

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

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

TABLE B
RANGE OF PHARMACOKINETIC PARAMETERS OF INTRAVENOUS FENTANYL IN PATIENTS

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

+Estimated

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

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

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

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

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

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

Pharmacodynamics

Analgesia

Fentanyl transdermal system 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 fentanyl transdermal system 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 fentanyl transdermal system. 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 fentanyl transdermal system, 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 fentanyl transdermal system. Fentanyl transdermal system is contraindicated in the treatment of postoperative and acute pain.

While most ~~adult and pediatric~~ patients using fentanyl transdermal system 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 fentanyl transdermal system. The use of initial doses in adults exceeding 25 μg/h is contraindicated in patients who are not tolerant to opioid therapy. A fentanyl transdermal system should only be administered to children if they are opioid-tolerant and age 2 years or older.

The use of fentanyl transdermal system 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 fentanyl transdermal system 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

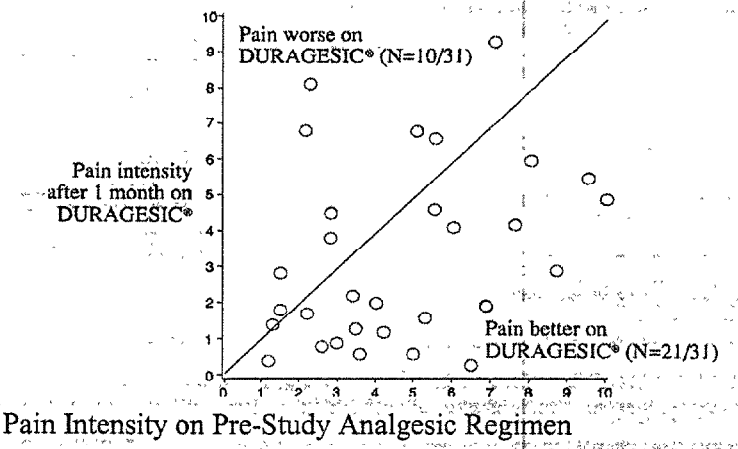
Adults

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

The analgesic efficacy of fentanyl transdermal system was demonstrated in an acute pain model with surgical procedures expected to produce various intensities of pain (eg, hysterectomy, major orthopedic surgery). Clinical use and safety was evaluated in patients experiencing chronic pain due to malignancy. Based on the results of these trials, fentanyl transdermal system 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, fentanyl transdermal system is contraindicated for postoperative analgesia. (See BOX WARNING, CLINICAL PHARMACOLOGY-Ventilatory Effects, and CONTRAINDICATIONS.)

Fentanyl transdermal system as therapy for pain due to cancer has been studied in 153 patients. In this patient population, fentanyl transdermal system has been administered in doses of 25 µg/h to 600 µg/h. Individual patients have used fentanyl transdermal system continuously for up to 866 days. At one month after initiation of fentanyl transdermal system 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 Fentanyl Transdermal System Use



[Replace "DURAGESIC® in the above figure with "Fentanyl Transdermal System.]

Pediatrics

The safety of fentanyl transdermal system 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 mcg/h and higher were used by 181 patients. Approximately 90% of the total daily opioid requirement (fentanyl transdermal system plus rescue medication) was provided by fentanyl transdermal system.

INDICATIONS AND USAGE

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.

Fentanyl transdermal system 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, fentanyl transdermal system is a safe and effective alternative to other opioid regimens. (See DOSAGE AND ADMINISTRATION.)

CONTRAINDICATIONS

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

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

Fentanyl transdermal system is also contraindicated in patients with known hypersensitivity to fentanyl or adhesives.

WARNINGS

The safety of fentanyl transdermal system has not been established in children under 2 years of age. A FENTANYL TRANSDERMAL SYSTEM 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 FENTANYL TRANSDERMAL SYSTEM REMOVAL SINCE SERUM FENTANYL CONCENTRATIONS DECLINE GRADUALLY AND REACH AN APPROXIMATE 50% REDUCTION IN SERUM CONCENTRATIONS 17 HOURS AFTER SYSTEM REMOVAL.

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

PRECAUTIONS

General

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

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

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

Hypoventilation (Respiratory Depression)

Hypoventilation may occur at any time during the use of fentanyl transdermal system. 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 fentanyl transdermal system. 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, fentanyl transdermal system should be administered with caution to patients with pre-existing medical conditions predisposing them to hypoventilation. In such patients, normal analgesic doses of opioids may further decrease respiratory drive to the point of respiratory failure.

Head Injuries and Increased Intracranial Pressure

Fentanyl transdermal system 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. Fentanyl transdermal system 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 fentanyl transdermal system 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 fentanyl transdermal system who develop fever should be monitored for opioid side effects and the fentanyl transdermal system dose should be adjusted if necessary.

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

Drug Interactions

Central Nervous System Depressants

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

Agents Affecting Cytochrome P450 3A4 Isoenzyme System

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

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

Drug or Alcohol Dependence

Use of fentanyl transdermal system in combination with alcoholic beverages and/or other CNS depressants can result in increased risk to the patient. fentanyl transdermal system 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 fentanyl transdermal system 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 fentanyl transdermal system 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. Fentanyl transdermal system should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery

Fentanyl transdermal system is not recommended for analgesia during labor and delivery.

Nursing Mothers

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

Pediatric Use

Fentanyl transdermal system was not studied in children under 2 years of age. Fentanyl transdermal system 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 fentanyl transdermal system (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 fentanyl transdermal system® 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 fentanyl transdermal system dispensed to the patient.

Disposal of fentanyl transdermal system

Fentanyl transdermal system should be kept out of the reach of children. Fentanyl transdermal 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 fentanyl transdermal system have been reported. (See BOX WARNING and CONTRAINDICATIONS.)

Pre-marketing Clinical Trial Experience:

In adults, the safety of fentanyl transdermal system has been evaluated in 357 postoperative patients and 153 cancer patients for a total of 510 patients. Patients with acute pain used fentanyl transdermal system for 1 to 3 days. The duration of fentanyl transdermal system use varied in cancer patients; 56% of patients used fentanyl transdermal system for over 30 days, 28% continued treatment for more than 4 months, and 10% used fentanyl transdermal system 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 fentanyl transdermal system was not always determined. The frequencies presented here reflect the actual frequency of each adverse effect in patients who received fentanyl transdermal system. 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 fentanyl transdermal system has been evaluated in 291 patients ages 2-18 years with chronic pain. The duration of fentanyl transdermal system 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 fentanyl transdermal system for at least 4 months and 9 patients for more than 9 months. There was no apparent pediatric-specific risk associated with fentanyl transdermal system use in children as young as 2 years old when used as directed.

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

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

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

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

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

* Reactions occurring in 3% - 10% of fentanyl transdermal system patients

** Reactions occurring in 10% or more of fentanyl transdermal system 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 fentanyl transdermal system administration is unknown. This information is listed to serve as alerting information for the physician.

Cardiovascular: bradycardia
Digestive: abdominal distention
Nervous: aphasia, hypertonia, vertigo, stupor, hypotonia, depersonalization, hostility
Respiratory: stertorous breathing, asthma, respiratory disorder
Skin and Appendages, General: exfoliative dermatitis, pustules
Special Senses: amblyopia
Urogenital: bladder pain, oliguria, urinary frequency

Post-Marketing Experience- Adults:

The following adverse reactions reported to have been observed in association with the use of fentanyl transdermal system and not reported in the pre-marketing adverse reactions section above include:

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

DRUG ABUSE AND DEPENDENCE

Fentanyl is a Schedule II controlled substance and can produce drug dependence similar to that produced by morphine. 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 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).

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 fentanyl transdermal system 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.

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

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

Each fentanyl transdermal system 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.

Fentanyl transdermal system 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 FENTANYL TRANSDERMAL SYSTEM APPLICATION. REDUCED DOSES OF FENTANYL TRANSDERMAL SYSTEM ARE SUGGESTED FOR THE ELDERLY AND OTHER GROUPS DISCUSSED IN PRECAUTIONS.

FENTANYL TRANSDERMAL SYSTEM DOSES GREATER THAN 25 mcG/H SHOULD NOT BE USED FOR INITIATION OF FENTANYL TRANSDERMAL SYSTEM THERAPY IN NON-OPIOID-TOLERANT PATIENTS. Pediatric patients converting to fentanyl transdermal system 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 fentanyl transdermal system dose, attention should be given to 1) the daily dose, potency, and characteristics of the opioid the patient has been taking previously (eg, whether it is a pure agonist or mixed agonist-antagonist), 2) the reliability of the relative potency estimates used to calculate the fentanyl transdermal system 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 Fentanyl Transdermal System Dose Selection

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

To convert patients from oral or parenteral opioids to fentanyl transdermal system 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 fentanyl transdermal system dose. Use this table to find the calculated 24-hour morphine dose and the corresponding fentanyl transdermal system dose. Initiate fentanyl transdermal system 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 fentanyl transdermal system is likely too low for 50% of patients. This starting dose is recommended to minimize the potential for overdosing patients with the first dose. For delivery rates in excess of 100 μg/h, multiple systems may be used.

Table C[a]

EQUIANALGESIC POTENCY CONVERSION

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

[Disclaimers for the proprietary names appearing in the Table will be included when the ANDA is submitted]

[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 FENTANYL TRANSDERMAL SYSTEM DOSE BASED UPON DAILY ORAL MORPHINE DOSE

Oral 24-hour Morphine (mg/day)	Fentanyl transdermal system 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 fentanyl transdermal system.

[1] THIS TABLE SHOULD NOT BE USED TO CONVERT FROM FENTANYL TRANSDERMAL SYSTEM TO OTHER THERAPIES, BECAUSE THIS CONVERSION TO FENTANYL TRANSDERMAL SYSTEM 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 FENTANYL TRANSDERMAL SYSTEM.)

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

The majority of patients are adequately maintained with fentanyl transdermal system 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 fentanyl transdermal system 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 fentanyl transdermal system cannot be made before 24 hours of wearing. The initial fentanyl transdermal system dosage may be increased after 3 days (see Dose Titration).

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

Dose Titration

The recommended initial fentanyl transdermal system 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 fentanyl transdermal system. The initial fentanyl transdermal system 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 fentanyl transdermal system 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 fentanyl transdermal system dose.

Discontinuation of fentanyl transdermal system

To convert patients to another opioid, remove fentanyl transdermal system 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 FENTANYL TRANSDERMAL SYSTEM TO OTHER THERAPIES. BECAUSE THE CONVERSION TO FENTANYL TRANSDERMAL SYSTEM 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

Fentanyl transdermal system is supplied in cartons containing 5 individually packaged systems. See chart for information regarding individual systems.

Fentanyl Transdermal System Dose (mcg/h)	System Size (cm^2)	Fentanyl Content (mg)	NDC Number
Fentanyl transdermal system-25	10	2.5	
Fentanyl transdermal system-37.5*	15	3.75	
Fentanyl transdermal system-50*	20	5	
Fentanyl transdermal system-62.5*	25	6.25	
Fentanyl transdermal system-75*	30	7.5	
Fentanyl transdermal system-87.5*	35	8.75	
Fentanyl transdermal system-100*	40	10	

*FOR USE ONLY IN OPIOID TOLERANT PATIENTS.

[information specific to the drug product will be included when the ANDA is submitted.]

Safety and Handling

Fentanyl transdermal system 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 fentanyl transdermal system. If the fentanyl transdermal system system is cut or damaged, controlled drug delivery will not be possible.

KEEP FENTANYL TRANSDERMAL SYSTEM 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.

[information specific to the drug product will be included when the ANDA is submitted.]

Patient Information

FENTANYL TRANSDERMAL SYSTEM (Schedule II symbol)

This leaflet contains important information about fentanyl transdermal system. Read this Patient Information carefully before you start using fentanyl transdermal system. 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 fentanyl transdermal system 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 fentanyl transdermal system?

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

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

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

What is fentanyl transdermal system?

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

[DIAGRAM SPECIFIC TO THE PROPOSED DRUG PRODUCT WILL BE SUBMITTED IN THE LABELIGN WHEN THE ANDA IS SUBMITTED]

Who should not use fentanyl transdermal system?

Do not use fentanyl transdermal system:

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

Before using fentanyl transdermal system, tell your health care provider if you:

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

Some medicines may cause serious side effects when used with fentanyl transdermal system. 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 fentanyl transdermal system need to be changed when used together.

What should I know about using fentanyl transdermal system in children?

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

How do I use fentanyl transdermal system?

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

What should I avoid while using fentanyl transdermal system?

- **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 fentanyl transdermal system to pass into your body.

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

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

- **DO NOT DRINK ANY ALCOHOL WHILE USING FENTANYL TRANSDERMAL SYSTEM.** 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 FENTANYL TRANSDERMAL SYSTEM AFFECTS YOU. FENTANYL TRANSDERMAL SYSTEM CAN MAKE YOU SLEEPY. ASK YOUR HEALTH CARE PROVIDER TO TELL YOU WHEN IT IS OKAY TO DO THESE ACTIVITIES.

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

What are the possible side effects of fentanyl transdermal system?

- **Fentanyl transdermal system can cause trouble breathing (hypoventilation) which can be dangerous and even lead to death if not treated.** This can happen if you use too much fentanyl transdermal system or the dose is too high for you. The signs and symptoms of hypoventilation include:

–Slow breathing
–Shallow breathing (little chest movement with breathing)
–Trouble breathing

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

- The most common side effects with fentanyl transdermal system 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 fentanyl transdermal system. For a complete list, ask your health care provider or pharmacist.

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

How and where to apply fentanyl transdermal system

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

1. **Prepare:** For adults, put the patch on the chest, back, flank (sides of the waist), or upper arm in a place where there is no hair. Put it on right away after you have removed it from the pouch. Avoid sensitive areas or those that move around a lot. If there is hair, **do not shave (shaving irritates the skin).** 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 fentanyl transdermal system patch is sealed in its own protective pouch. Do not remove the fentanyl transdermal system patch from the pouch until you are ready to use it. When you are ready to put on fentanyl transdermal system, tear open the pouch along the dotted line, starting at the slit, and remove the fentanyl transdermal system patch.

- Do not put the fentanyl transdermal system 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.

- Fentanyl transdermal system 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 fentanyl transdermal system").

- Wash your hands when you have finished applying fentanyl transdermal system.

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

When to apply fentanyl transdermal system

- You can apply fentanyl transdermal system 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 fentanyl transdermal system patch to the same place where you removed the last fentanyl transdermal system patch.
- Your health care provider may increase your fentanyl transdermal system dose if your pain is not controlled well. **If you continue to have pain, call your health care provider.**

Water and fentanyl transdermal system

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

Disposing of fentanyl transdermal system

- BEFORE PUTTING ON A NEW FENTANYL TRANSDERMAL SYSTEM PATCH, REMOVE THE PATCH YOU HAVE BEEN WEARING.

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

- THROW AWAY ANY FENTANYL TRANSDERMAL SYSTEM 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 fentanyl tansdermal system

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

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

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

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

How should fentanyl transdermal system be stored?

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

GENERAL INFORMATION ABOUT THE SAFE AND EFFECTIVE USE OF FENTANYL TRANSDERMAL SYSTEM

MEDICINES ARE SOMETIMES PRESCRIBED FOR CONDITIONS THAT ARE NOT MENTIONED IN PATIENT INFORMATION LEAFLETS. DO NOT USE FENTANYL TRANSDERMAL SYSTEM FOR A CONDITION FOR WHICH IT WAS NOT PRESCRIBED. DO NOT GIVE FENTANYL TRANSDERMAL SYSTEM TO OTHER PEOPLE, EVEN IF THEY HAVE THE SAME SYMPTOMS YOU HAVE. IT MAY BE DANGEROUS FOR THEM, AND IT IS AGAINST THE LAW.

KEEP FENTANYL TRANSDERMAL SYSTEM OUT OF THE REACH OF CHILDREN AND PETS.

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

[INFORMATION SPECIFIC TO A METHOD TO REACH THE MANUFACTURER REGARDING THE DRUG PRODUCT WILL BE INCLUDED WHEN THE ANDA IS SUBMITTED.]

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

WHAT ARE THE INGREDIENTS OF FENTANYL TRANSDERMAL SYSTEM?

ACTIVE INGREDIENT: FENTANYL

[*INFORMATION SPECIFIC TO THE DRUG PRODUCT WILL BE INCLUDED WHEN THE ANDA IS SUBMITTED.*]

RX ONLY

[INFORMATION SPECIFIC TO THE DRUG PRODUCT WILL BE INCLUDED WHEN THE ANDA IS SUBMITTED .]