

LACHMAN CONSULTANT SERVICES, INC.
CONSULTANTS TO THE PHARMACEUTICAL AND ALLIED INDUSTRIES

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November 4, 2002

OVERNIGHT COURIER 11/04/02

Dockets Management Branch
Food and Drug Administration (HFA-305)
Department of Health and Human Services
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Citizen Petition

Dear Sir or Madam:

The undersigned submits this petition, in quadruplicate, pursuant to section 505(j)(2)(C) of the Federal Food, Drug and Cosmetic Act and in accordance with 21 CFR 10.30 on behalf of a client requesting the Commissioner of the Food and Drug Administration to declare that the drug product, Fentanyl Transdermal System, 12.5 mcg/hr is suitable for consideration in an Abbreviated New Drug Application (ANDA).

A. Action Requested

The petitioner requests that the Commissioner of the Food and Drug Administration declare that Fentanyl Transdermal System, 12.5 mcg/hr is suitable for submission in an ANDA. The designated reference listed drug product upon which this petition is based is Duragesic® (Fentanyl Transdermal System) 25 mcg/hr, 50 mcg/hr, 75 mcg/hr and 100 mcg/hr manufactured by Alza Corporation (see listing of the Duragesic® application number NDA 19-813 on page 3-158 of the 22nd Edition of the Approved Drug Products with Therapeutic Equivalence Evaluations (Orange Book) (Attachment 1)). Therefore, the petitioner seeks a change in strength (from a 25 mcg/hr, 50 mcg/hr, 75 mcg/hr and 100 mcg/hr product to include a 12.5 mcg/hr strength transdermal system) from that of the listed drug product for use in providing the ability to titrate a patient to a required dose between two currently approved doses.

B. Statement of Grounds

The reference listed drug (RLD) product is currently available in strengths of 25 mcg/hr, 50 mcg/hr, 75 mcg/hr and 100 mcg/hr of Fentanyl. The proposed drug product represents a transdermal system that contains a lower strength of the drug product (12.5 mcg/hr) that when used in conjunction with a strength that is currently approved will provide a dose midway between the currently approved and available strengths. This additional proposed strength is consistent with the currently approved RLD product's labeling. Duragesic's approved labeling indicates that the product should be titrated to control pain and that "each patient should be maintained at the lowest dose providing acceptable pain control". The availability of a 12.5 mcg/hr product will provide greater flexibility in regard to selecting an appropriate specific intermediate dose that will provide the needed pain relief as determined by the prescribing

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physician and dictated by individual patient's condition and response. The petition is thus seeking a change in strength (from the existing 25 mcg/hr, 50 mcg/hr, 75 mcg/hr and 100 mcg/hr transdermal systems to include a 12.5 mcg/hr product) from that of the reference-listed drug.

The approved labeling of the RLD provides that the dose of Fentanyl must be carefully individualized for each patient due to the potential for serious or life-threatening hypoventilation. This potent narcotic agent 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.**

Contraindications for starting doses exceeding 25 mcg/hr at the initiation of opioid therapy are also outlined in a Black Box Warning. Therefore, for non-opioid tolerant patients, starting doses above 25 mcg/hr are clearly not appropriate.

In addition the labeling clearly states that:

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.

The usually initial dosage for non-opioid tolerant patients is **not to exceed** 25 mcg/hr. For initial dose selection for opioid tolerant patients, the labeling of the reference-listed drug product provides a conversion table based on the equianalgesic potency of various oral or parenteral opioid products. The physician is provided a table that relates the current daily oral morphine equivalent dose to a recommended initial Duragesic® dose. This chart can be found in the labeling of the reference-listed drug.

The above-referenced conversion chart lists Fentanyl dosage recommendations based on a total daily morphine equivalent dose. The dose equivalents suggested for Fentanyl dose selection represent a fairly wide range of morphine equivalent doses that are equated to each currently available strength of Fentanyl transdermal systems. In addition, the labeling of the reference-listed drug product cautions that the recommended starting dose may be too low for 50% of the patients. The availability of a 12.5 mcg/hr transdermal system may offer an alternative intermediate dosage based on patient response by adding a 12.5 mcg/hr system to an existing currently approved strength.

Likewise, because of the potentially fatal side effects of Fentanyl, extreme care must be taken in titrating a patient to an effective tolerable dose. Dosing instructions in the RLD advise that doses must be individualized, based upon the status of each patient and should be assessed at regular intervals after Fentanyl Transdermal System application. The patient should be maintained at the lowest dose providing acceptable pain control. The inclusion of a 12.5 mcg/hr strength product would allow the physician additional flexibility in providing appropriate intermediate doses not available by use of the currently approved strengths for certain patients.

For instance, in a case where a patient's pain is not adequately controlled on a 25 mcg/hr patch, the physician's only current option would be to increase the patient's dose two fold to a 50 mcg/hr patch or add supplemental opioid therapy. However, if the 50 mcg/hr system produces undesirable side effects or the addition of supplemental oral opioid therapy is precluded by intolerance due to severe nausea or vomiting or dysphasia, the availability to reach an intermediate dose by adding a 12.5 mcg/hr transdermal patch to the regimen to provide a dose between the 25 and 50 mcg/hr dose (or between any of the currently approved patch strengths) may provide the necessary increase in pain control while avoiding any undesirable side effects.

The application of multiple systems (patches) to achieve the desired dose is also contemplated in the RLD product's labeling. While the labeling of the RLD indicates that multiple systems may be applied for doses in excess of 100 mcg/hr, this is because the systems are available only in multiples of 25 mcg/hr. This would certainly imply that it would also be appropriate to utilize a second system to titrate a patient to an intermediate dose if one were available.

Copies of labeling of the reference-listed drug product upon which this petition is based and proposed draft labeling for the proposed product are included in Attachments 2 and 3, respectively. The proposed labeling is the "same as" that of the RLD labeling with the exception changes allowed because the manufacturer of the generic product differs. The How Supplied section that lists the additional proposed strength will also be changed, as well as instructions for the use of a 12.5 mcg system to achieve an intermediate dose. These changes are clearly authorized by the regulations that permit differences in labeling based on an approved petition under 21 CFR 314.98. There are, however, no changes in the indications, uses or warnings from that of the reference-listed drug product.

Pursuant to 21 CFR 314.55 (a), the proposed change in strength does not constitute a request to file an application for a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration. Therefore, the petitioner believes that the proposed product does not fall under the requirement for an assessment of safety and efficacy in pediatric patients.

Therefore, the petitioner requests that the Commissioner find that a change in strength from a 25 mcg/hr, 50 mcg/hr, 75 mcg/hr and 100 mcg/hr transdermal systems of Fentanyl to include a strength of 12.5 mcg/hr to achieve an intermediate dose mid-way between two currently approved doses for this product raise no questions of safety or effectiveness, and the Agency should, therefore, approve the petition.

C. Environmental Impact

The petitioner claims a categorical exclusion under 21 CFR 25.31.

D. Economic Impact

The petitioner does not believe that this is applicable in this case, but will agree to provide such an analysis if requested by the Agency.

E. Certification

The undersigned certifies, that to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner, which are unfavorable to the petition.

Respectfully submitted,



Robert. W. Pollock *pk*
Vice President
Lachman Consultant Services, Inc.
1600 Stewart Avenue
Westbury, New York 11590

RWP/pk

Attachments

cc: G. Davis (OGD)
M. Shimer (OGD)
L. Lachman

M33P2308

LACHIMAN CONSULTANT SERVICES, INC.
Westbury, NY 11590

ATTACHMENT 1

PRESCRIPTION DRUG PRODUCT LIST

3-158

FENTANYL

FILM, EXTENDED RELEASE; TRANSDERMAL
DURAGESIC

+ ALZA	0.6MG/24HR	N19813 004	
		AUG 07, 1990	
	1.2MG/24HR	N19813 003	
		AUG 07, 1990	
	1.8MG/24HR	N19813 002	
		AUG 07, 1990	
	2.4MG/24HR	N19813 001	
		AUG 07, 1990	

FENTANYL CITRATE

INJECTABLE; INJECTION

FENTANYL CITRATE

<u>AP</u>	ABBOTT	<u>EQ 0.05MG BASE/ML</u>	<u>N19115 001</u>
			JAN 12, 1985
<u>AP</u>	ABBOTT	<u>EQ 0.05MG BASE/ML</u>	<u>N72786 001</u>
			SEP 24, 1991
<u>AP</u>	+ ELKINS SINN	<u>EQ 0.05MG BASE/ML</u>	<u>N19101 001</u>
			JUL 11, 1984
<u>AP</u>	+ AKORN MFG	<u>EQ 0.05MG BASE/ML</u>	<u>N16619 001</u>

TROCHE/LOZENGE; ORAL

ACTIQ

ANESTA

EQ 0.2MG BASE	N20747 001	
	NOV 04, 1998	
EQ 0.4MG BASE	N20747 002	
	NOV 04, 1998	
EQ 0.6MG BASE	N20747 003	
	NOV 04, 1998	
EQ 0.8MG BASE	N20747 004	
	NOV 04, 1998	
EQ 1.2MG BASE	N20747 005	
	NOV 04, 1998	
+ EQ 1.6MG BASE	N20747 006	
	NOV 04, 1998	
EQ 0.1MG BASE	N20195 007	
	OCT 30, 1995	
EQ 0.2MG BASE	N20195 001	
	OCT 04, 1993	
EQ 0.3MG BASE	N20195 002	
	OCT 04, 1993	

FENTANYL
ANESTA

FENTANYL CITRATE

TROCHE/LOZENGE; ORAL

FENTANYL

+ ANESTA	EQ 0.4MG BASE	N20195 003
		OCT 04, 1993

FENTANYL CITRATE; *MULTIPLE*
SEE DROPERIDOL; FENTANYL CITRATE

FERRIC AMMONIUM CITRATE

FOR SOLUTION; ORAL

FERRISELTZ

+ AMERSHAM HLTH	600MG/PACKET	N20292 001
		OCT 14, 1997

FERUMOXIDES

INJECTABLE; INJECTION

FERIDEX I.V.

+ ADV MAGNETICS	EQ 11.2MG IRON/ML	N20416 001
		AUG 30, 1996

FERUMOXISIL

SUSPENSION; ORAL

GASTROMARK

+ ADV MAGNETICS	EQ 0.175MG IRON/ML	N20410 001
		DEC 06, 1996

FEXOFENADINE HYDROCHLORIDE

CAPSULE; ORAL

ALLEGRA

+ AVENTIS PHARMS	60MG	N20625 001
		JUL 25, 1996

TABLET; ORAL

ALLEGRA

AVENTIS PHARMS	30MG	N20872 001
		FEB 25, 2000
	60MG	N20872 002
		FEB 25, 2000

LACHMAN CONSULTANT SERVICES, INC.
Westbury, NY 11590

ATTACHMENT 2

PATIENT PACKAGE INSERT (FRONT)



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When to Apply DURAGESIC®

If you need continued pain control, wear DURAGESIC® continuously for three days (approximately 72 hours), or as directed by your doctor and then remove the patch and replace it as directed by your doctor. Do not apply the new DURAGESIC® to the same place where you removed the last DURAGESIC®.

Your doctor may increase your DURAGESIC® dose if your pain is not adequately controlled. IF YOU CONTINUE TO HAVE PAIN CALL YOUR DOCTOR.

Water and DURAGESIC®

You can bathe, swim or shower while you are wearing DURAGESIC®. If the patch does fall off, put a new DURAGESIC® on your skin. Before putting on a new DURAGESIC®, make sure the new skin area you have selected is dry.

Disposing of DURAGESIC®

Before putting on a new DURAGESIC®, remove the patch you have been wearing. Fold the used DURAGESIC® in half so that the sticky side sticks to itself. Flush the used DURAGESIC® down the toilet immediately. Even used DURAGESIC® patches contain enough fentanyl to poison infants, children, pets, and adults who have not been prescribed DURAGESIC®.

Throw away any DURAGESIC® patches that are left over from your prescription as soon as they are no longer needed. Remove the leftover patches from their protective pouch and remove the protective liner. Fold the patches in half and flush the patch down the toilet. Do not flush the pouch or the protective liner.

Safety and Handling

DURAGESIC® is supplied 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 DURAGESIC®. Do not use the DURAGESIC® patch if it is damaged in any way. DURAGESIC® will not work properly or may not be safe to use if it is cut or damaged. Too much drug may be released too quickly 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 dislodges and accidentally adheres to the skin of another person, take the patch off immediately and call a doctor.

Storage Instructions

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

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

Do not store DURAGESIC® above 77° F (25° C). Remember, the inside of your car can reach temperatures much higher than this in the summer.

For questions concerning this product please call the JANSSEN Customer Action Center at 1-800-JANSSEN (1-800-526-7736) 8A.M. to 8P.M. EST, Monday through Friday.

Manufactured by:
ALZA Corporation
Palo Alto, CA 94304

Distributed by:
JANSSEN PHARMACEUTICA, INC.
Titusville, NJ 08560



JANSSEN
PHARMACEUTICA

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April 1997, April 1998

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DURAGESIC®
(FENTANYL
TRANSDERMAL
SYSTEM) **II**

Patient Instructions

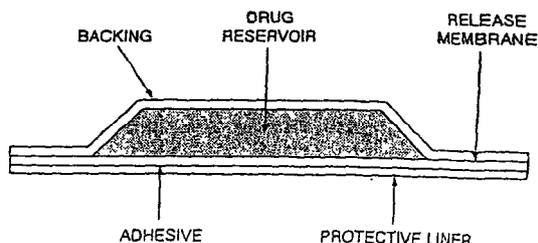


This leaflet gives a summary of information about DURAGESIC® and will provide you with specific information about how to use DURAGESIC®. If you have any questions or want more information, be sure to discuss your question with your doctor or other health professional. You could ask them for a copy of the information on this product written for health professionals if you wish.

What is DURAGESIC®?

DURAGESIC® is a thin, adhesive, rectangular patch that is worn on your skin. DURAGESIC® delivers a strong pain-relieving medicine called "fentanyl" through the skin and into the bloodstream. It should only be used to relieve severe pain that will last more than a few days (chronic pain). It should only be used when other less strong medicines have not been effective and when pain needs to be controlled around the clock.

DURAGESIC® is NOT INTENDED FOR USE if you have pain that will go away in a few days, such as pain from surgery, medical or dental procedures, or short-lasting painful conditions.



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PATIENT PACKAGE INSERT (BACK)

WHAT ARE THE IMPORTANT SIDE EFFECTS AND PRECAUTIONS?

Before using DURAGESIC[®], you and your household members need to be aware of some important information about using this drug. You should discuss with your doctor the most important side effects of this drug prior to your using it. **ALWAYS FEEL FREE TO CONTACT YOUR DOCTOR WITH ANY QUESTIONS OR CONCERNS YOU MAY HAVE ABOUT DURAGESIC[®] AND ANY SUSPECTED SIDE EFFECTS.**

SOME OF THE IMPORTANT THINGS TO HELP YOU USE THIS MEDICATION PROPERLY INCLUDE:

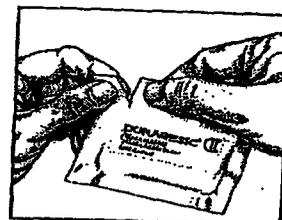
- (1) One important side effect is slow, shallow, and/or difficulty in breathing, which can occur if the dose of DURAGESIC[®] is too high. You and your household members should discuss with your doctor what signs and symptoms to look for and what to do if these develop. If you are uncertain what to do, call your doctor or get other emergency medical help.
- (2) Do not take other medications (prescription or over-the-counter) while wearing DURAGESIC[®] unless specifically told to do so by your doctor. Be especially careful about drugs that can make you sleepy.
- (3) Do not drink alcohol while wearing the patch. Also do not drive a vehicle or operate dangerous machinery unless specifically told that you may do so by your doctor.
- (4) Direct sources of heat may increase the amount of medication you receive through the skin from the patch. Do not use electric blankets, heating pads, sun lamps, heated water beds, or other sources of direct heat on a patch. Avoid sun bathing, long hot baths, or other sources of heat to the body.
- (5) If you develop a fever greater than 102° F, contact your doctor because the increased fever could cause you to receive more medication than you should from the patch.
- (6) Do not wear more than one patch at a time unless specifically told to do so by your doctor.
- (7) Do not use this patch if you are nursing an infant unless specifically told to do so by your doctor. The medication can get into human milk and can cause serious problems for the infant.
- (8) DURAGESIC[®] should not be used by children less than 12 years old or patients less than 18 years old who weigh less than 110 pounds, unless your doctor has enrolled the patient in an authorized research program.
- (9) Be sure to dispose of used and unused patches so they cannot be touched by any other people or pets.

How and Where to Apply DURAGESIC[®]

In the hospital, your doctor or another qualified medical person will apply DURAGESIC[®] for you. At home, you or a member of your family may apply DURAGESIC[®] to your skin.

Step 1

Each DURAGESIC[®] is sealed in its own protective pouch. Until you are ready to use DURAGESIC[®], do not remove it from the pouch. When you are ready to put on DURAGESIC[®], tear open the pouch and remove the DURAGESIC[®] patch.



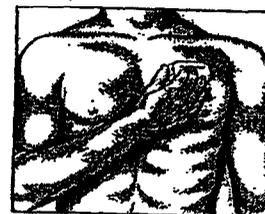
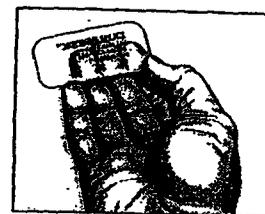
Step 2

A stiff, protective liner covers the sticky side of the DURAGESIC[®] — the side that will be put on your skin. With the oversized, stiff, clear liner facing you, pull the liner from the DURAGESIC[®] patch (try to touch the sticky side as little as possible). Throw away the liner.



Step 3

Immediately after you have taken DURAGESIC[®] from the pouch, apply the sticky side of the DURAGESIC[®] to a non-hairy, dry area of your chest, back, flank or upper arm. If the area you select has body hair, clip (do not shave) the hair close to the skin with scissors. Do not put DURAGESIC[®] on skin that is excessively oily, burned, broken out, cut, irritated or damaged in any way. If you need to clean the skin where the patch will be applied, use only clear water. Do not use soaps, oils, lotions, alcohol or other products that might irritate the skin under the patch. Make sure that the skin is completely dry. Press the DURAGESIC[®] firmly on your skin with the palm of your hand for about 30 seconds. Make sure it sticks well to your skin, especially around the edges of the patch.



Not all adhesive products stick to all patients. If the patch does not stick well or loosens after application, tape the edges down with first aid tape. In the event that the patch falls off, discard it and put a new one on a different skin site. (See Disposing of DURAGESIC[®].)

Step 4

Wash your hands when you have finished applying DURAGESIC[®].

Step 5

After wearing DURAGESIC[®] for three days, remove it (see Disposing of DURAGESIC[®]). Then choose a *different* place on your skin to apply a new DURAGESIC[®] and repeat Steps 1 to 4, in order.

DURAGESIC®
(FENTANYL
TRANSDERMAL
SYSTEM) **II**

Full Prescribing Information

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.)

DURAGESIC® SHOULD NOT BE ADMINISTERED TO CHILDREN UNDER 12 YEARS OF AGE OR PATIENTS UNDER 18 YEARS OF AGE WHO WEIGH LESS THAN 50 KG (110 LBS) EXCEPT IN AN AUTHORIZED INVESTIGATIONAL RESEARCH SETTING.
(See PRECAUTIONS - Pediatric Use.)

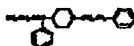
DURAGESIC® is indicated for treatment of chronic pain (such as that of malignancy) that:

- 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 C₂₃H₂₈N₂O. 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 cm²). The composition per unit area of all system sizes is identical. Each system also contains 0.1 mL of alcohol USP per 10 cm².

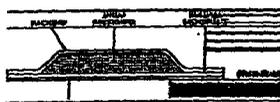
Dose* (µg/h)	Size (cm ²)	Fentanyl Content (mg)
25	10	2.5
50**	20	5
75**	30	7.5
100**	40	10

*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.

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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)

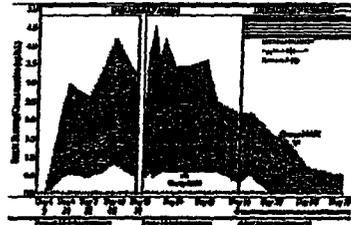
DURAGESIC® (fentanyl transdermal system) releases fentanyl from the reservoir at a nearly constant amount per unit time. The concentration gradient existing between the saturated solution of drug in the reservoir and the lower concentration in the skin drives drug release. Fentanyl moves in the direction 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) are 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 fluctuations, 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). The average clearance in patients undergoing various surgical procedures is 46 L/h (range 27-75, N=8). 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 97% 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 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 manifest by respiratory rates of less than 8 breaths/minute or a pCO₂ 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 non-tolerant 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 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 exceeding 25 µg/h is contraindicated in patients who are not tolerant to opioid therapy. 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.

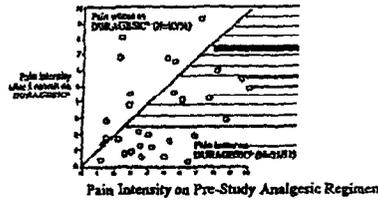
CLINICAL TRIALS

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 (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, 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



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-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.

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

WARNINGS

DURAGESIC® (FENTANYL TRANSDERMAL SYSTEM) SHOULD NOT BE ADMINISTERED TO CHILDREN UNDER 12 YEARS OF AGE OR PATIENTS UNDER 18 YEARS OF AGE WHO WEIGH LESS THAN 50 KG (110 LBS) EXCEPT IN AN AUTHORIZED INVESTIGATIONAL RESEARCH SETTING. (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 SHOULD BE ADVISED TO AVOID EXPOSING THE DURAGESIC® APPLICATION SITE TO DIRECT EXTERNAL HEAT SOURCES, SUCH AS HEATING PADS OR ELECTRIC BLANKETS, HEAT LAMPS, SAUNAS, HOT TUBS, AND HEATED WATER BEDS, ETC., WHILE WEARING THE SYSTEM. THERE IS A POTENTIAL FOR TEMPERATURE-DEPENDENT INCREASES IN FENTANYL RELEASE FROM THE SYSTEM. (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. (See BOX WARNING.)

DURAGESIC® may impair mental and/or physical ability required for the performance of potentially hazardous tasks (eg. 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 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 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® (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

DURAGESIC® should not be used in patients who may be particularly susceptible to the intracranial effects of CO₂ retention such as those with evidence of increased intracranial pressure, impaired consciousness, or coma. Opioids may obscure the clinical course of patients with head injury. DURAGESIC® should be used with caution in patients with brain tumors.

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

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 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 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

The safety and efficacy of DURAGESIC® in pediatric patients have not been established. (See BOX WARNING and CONTRAINDICATIONS.)

DURAGESIC® SHOULD NOT BE ADMINISTERED TO CHILDREN UNDER 12 YEARS OF AGE OR PATIENTS UNDER 18 YEARS OF AGE WHO WEIGH LESS THAN 50 KG (110 LBS) EXCEPT IN AN AUTHORIZED INVESTIGATIONAL RESEARCH SETTING.

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.

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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:

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-naïve 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.

The following adverse reactions were reported in 153 cancer patients at a frequency of 1% or greater; similar reactions were seen in the 357 postoperative patients studied.

Body as a Whole: abdominal pain*, headache*

Cardiovascular: arrhythmia, chest pain

Digestive: nausea**, vomiting**, constipation**, dry mouth**, anorexia*, diarrhea*, dyspepsia*, flatulence

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

Respiratory: dyspnea*, hypoventilation*, apnea*, hemoptysis, pharyngitis, hiccup

Skin and Appendages: sweating**, pruritus*, rash, application site reaction - erythema, papules, itching, edema

Urogenital: 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 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:

The following adverse reactions reported to have been observed in association with the use of DURAGESIC® 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. 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 overdose 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.

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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. 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 (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 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.

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 (eg, 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 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

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)
heroin	5	60
meperidine (Demerol®)	75	—
codene	130	200

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- ^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 D¹
RECOMMENDED INITIAL DURAGESIC[®]
DOSE BASED UPON DAILY ORAL MORPHINE DOSE

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

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

¹ 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[®].)

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. 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 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 μ g/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 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 ($\mu\text{g/h}$)	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

DRA order form required. A schedule CII narcotic.

Manufactured by:
ALZA Corporation,
Mountain View, CA 94043

7500315
Revised January 2000, February 2001
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Distributed by:
Janssen Pharmaceutica Products, L.P.
Titusville, NJ 08560



LACHMAN CONSULTANT SERVICES, INC.
Westbury, NY 11590

ATTACHMENT 3

FENTANYL TRANSDERMAL SYSTEM

Full Prescribing Information

Rx Only

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 outpatient surgeries**
- **In the management of mild or intermittent pain responsive to PRN or non-opioid therapy**
- **In doses exceeding 25 mcg/hr at the initiation of opioid therapy**

(See CONTRAINDICATIONS for further information.)

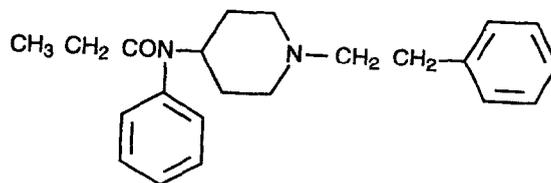
FENTANYL TRANSDERMAL SYSTEM SHOULD NOT BE ADMINISTERED TO CHILDREN UNDER 12 YEARS OF AGE OR PATIENTS UNDER 18 YEARS OF AGE WHO WEIGH LESS THAN 50 KG (110 LBS) EXCEPT IN AN AUTHORIZED INVESTIGATIONAL RESEARCH SETTING. (See PRECAUTIONS – Pediatric Use.)

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 50, 75 and 100 mcg/hr dosages should ONLY be used in patients who are already 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 structure 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/hr per 6.25 cm²). The composition per unit area of all system sizes is identical.

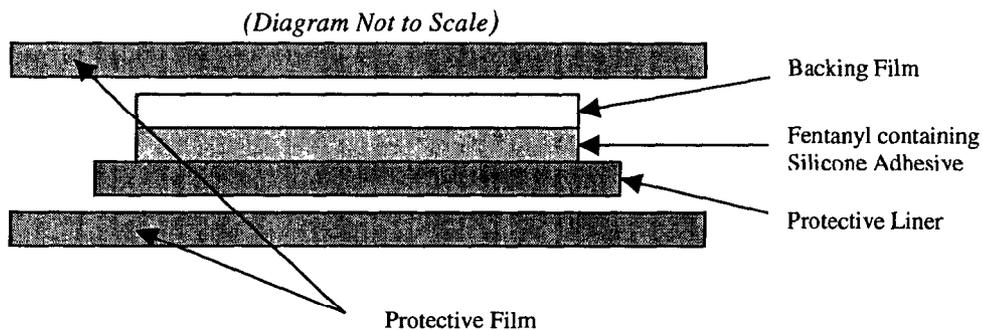
Dose* (mcg/hr)	Size (cm ²)	Fentanyl Content (mg)
12.5	3.13	1.28
25	6.25	2.55
50**	12.5	5.10
75**	18.75	7.65
100**	25	10.20

* Nominal delivery rate per hour

** FOR USE ONLY IN OPIOID TOLERANT PATIENTS

Fentanyl transdermal system is a translucent rectangular patch with rounded corners comprising a protective liner and two functional layers. Proceeding from the outer surface toward the surface adhering to skin, these layers are: 1) a backing layer of polyolefin film; and 2) a fentanyl containing silicone adhesive layer. Before use, a protective liner that is attached to and covering the adhesive layer is removed and discarded.

Fentanyl transdermal systems are packaged with additional pieces of protective film above and below the system within each pouch. These are also discarded at the time of use.



The active component of the system is fentanyl. The remaining components are pharmacologically inactive.

Do not cut or damage the fentanyl transdermal system. If the fentanyl transdermal 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 mcg/kg.

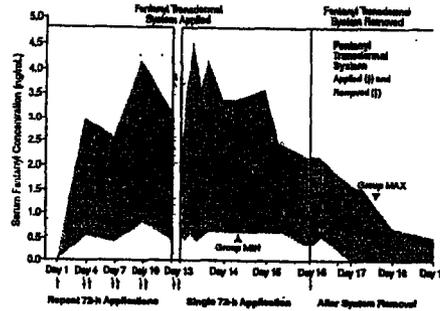
Pharmacokinetics (see graph and tables): Fentanyl transdermal system releases fentanyl from the adhesive matrix at a nearly constant amount per unit time. The concentration gradient existing between the adhesive matrix and the lower concentration in the skin drives drug release. Fentanyl moves in the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

While there is variation in dose delivered among patients, the nominal flux of the systems (12.5, 25, 50, 75 and 100 mcg of fentanyl per hour) are sufficiently accurate as to allow individual titration of dosage for a given patient.

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 to 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 to 12) hours.

**Serum Fentanyl Concentrations
Following Multiple Applications of
Fentanyl Transdermal System 100 mcg/hr (n = 10)**



**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 mcg/hr	38.1 (18.0)	0.6 (0.3)
Fentanyl Transdermal System 50 mcg/hr	34.8 (15.4)	1.4 (0.5)
Fentanyl Transdermal System 75 mcg/hr	33.5 (14.5)	1.7 (0.7)
Fentanyl Transdermal System 100 mcg/hr	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 to 75	3 to 8	3 to 12
Hepatically Impaired Patients	3 to 80 ⁺	0.8 to 8 ⁺	4 to 12 ⁺
Renally Impaired Patients	30 to 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 to 8, N=8). The average clearance in patients undergoing various surgical procedures is 46 L/h (range 27 to 75, N=8). 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 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 mcg/hr in an acute pain model.

Minimum effective analgesic serum concentrations of fentanyl in opioid naive 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 manifest by respiratory rates of less than 8 breaths/minute or a pCO₂ 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-naïve postoperative 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 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 exceeding 25 mcg/hr is contraindicated in patients who are not tolerant to opioid therapy. 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%.

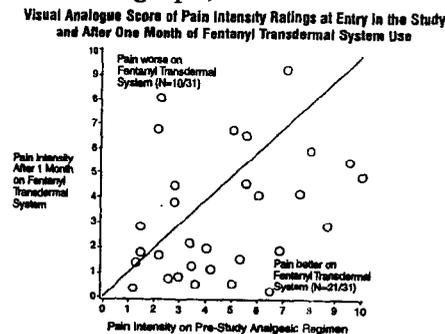
CNS Effects: In opioid naïve patients, central nervous system effects increase when serum fentanyl concentrations are greater than 3 ng/mL.

CLINICAL TRIALS: 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 mcg/hr to 600 mcg/hr. 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 pre-study analgesic regimen of oral morphine (see graph).



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 mcg/hr 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: FENTANYL TRANSDERMAL SYSTEM SHOULD NOT BE ADMINISTERED TO CHILDREN UNDER 12 YEARS OF AGE OR PATIENTS UNDER 18 YEARS OF AGE WHO WEIGH LESS THAN 50 KG (110 LBS) EXCEPT IN AN AUTHORIZED INVESTIGATIONAL RESEARCH SETTING. (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 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/hr 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. (See BOX WARNING.)

Fentanyl transdermal system 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 fentanyl transdermal system should not drive or operate dangerous machinery unless they are tolerant to the side effects of the drug.

Patients 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 CO₂ retention such as those with evidence of increased intracranial pressure, impaired consciousness, or coma. Opioids may obscure the clinical course of patients with head injury. 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 systems who develop fever should be monitored for opioid side effects and the fentanyl transdermal system dose should be adjusted if necessary.

ALL PATIENTS 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., ritonavir) while receiving fentanyl transdermal system 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 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 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: The safety and efficacy of fentanyl transdermal system in pediatric patients have not been established. (See BOX WARNING and CONTRAINDICATIONS.)

FENTANYL TRANSDERMAL SYSTEM SHOULD NOT BE ADMINISTERED TO CHILDREN UNDER 12 YEARS OF AGE OR PATIENTS UNDER 18 YEARS OF AGE WHO WEIGH LESS THAN 50 KG (110 LBS) EXCEPT IN AN AUTHORIZED INVESTIGATIONAL RESEARCH SETTING.

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 25mcg/hr 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 systems 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.

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: 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-naïve 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.

The following adverse reactions were reported in 153 cancer patients at a frequency of 1% or greater; similar reactions were seen in the 357 postoperative patients studied.

Body as a Whole: abdominal pain*, headache*

Cardiovascular: arrhythmia, chest pain

Digestive: nausea**, vomiting**, constipation**, dry mouth**, anorexia*, diarrhea*, dyspepsia*, flatulence

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

Respiratory: dyspnea*, hypoventilation*, apnea*, hemoptysis, pharyngitis, hiccups

Skin and Appendages: sweating**, pruritus*, rash, application site reaction – erythema, papules, itching, edema

Urogenital: urinary retention*

* Reactions occurring in 3% to 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 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: 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 overdose 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 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 healthcare 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. 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 (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 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/HR SHOULD NOT BE USED FOR INITIATION OF FENTANYL TRANSDERMAL SYSTEM THERAPY IN NON-OPIOID-TOLERANT PATIENTS.

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 (e.g., 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, 12.5 mcg/hr, 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. A combination of the 12.5 mcg/hr and any of the 25, 50, 75 mcg/hr systems maybe used to achieve the appropriate delivery rate. For delivery rates in excess of 100 mcg/hr, 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)
Heroin	5	60
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. NEJM313(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 D¹
RECOMMENDED INITIAL FENTANYL TRANSDERMAL SYSTEM DOSE BASED UPON DAILY ORAL MORPHINE DOSE

Oral 24-hour Morphine (mg/day)	Fentanyl Transdermal System Dose (mcg/hr)
45-134	25
135-224	50
225-314	75
315-404	100
405-494	125
495-584	150
585-674	175
675-764	200
765-854	225
855-944	250
945-1034	275
1035-1124	300

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

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. 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 45 mg/24 hours of oral morphine to a 12.5 mcg/hr 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 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. OVERDOAGE 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/hr)	System Size (cm²)	Fentanyl Content (mg)
Fentanyl Transdermal System -12.5		3.13	1.28
Fentanyl Transdermal System -25		6.25	2.55
Fentanyl Transdermal System -50*		12.5	5.10
Fentanyl Transdermal System -75*		18.75	7.65
Fentanyl Transdermal System -100*		25	10.20

* FOR USE ONLY IN OPIOID TOLERANT PATIENTS

Safety and Handling: Do not cut or damage fentanyl transdermal system. If the fentanyl transdermal system is cut or damaged, controlled drug delivery will not be possible.

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

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

DEA order form required. A schedule CII narcotic.

Revised October 2002

FENTANYL TRANSDERMAL SYSTEM



Rx only

Patient Instructions

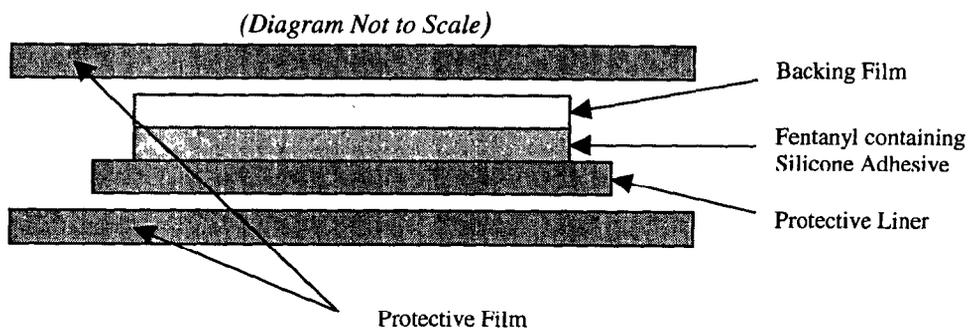
PLEASE READ THIS LEAFLET CAREFULLY BEFORE YOU USE FENTANYL TRANSDERMAL SYSTEM

This leaflet gives a summary of information about fentanyl transdermal system and will provide you with specific information about how to use fentanyl transdermal system. If you have any questions or want more information, be sure to discuss your question with your doctor or other health professional. You could ask them for a copy of the information on this product written for health professionals if you wish.

What is Fentanyl Transdermal System?

Fentanyl transdermal system is a thin, adhesive, rectangular patch with rounded corners that is worn on your skin. Fentanyl transdermal system delivers a strong pain-relieving medicine called “fentanyl” through the skin and into the bloodstream. It should only be used to relieve severe pain that will last more than a few days (chronic pain). It should only be used when other less strong medicines have not been effective and when pain needs to be controlled around the clock.

FENTANYL TRANSDERMAL SYSTEM is NOT INTENDED FOR USE if you have pain that will go away in a few days, such as pain from surgery, medical or dental procedures, or short-lasting painful conditions.



WHAT ARE THE IMPORTANT SIDE EFFECTS AND PRECAUTIONS?

Before using fentanyl transdermal system, you and your household members need to be aware of some important information about using this drug. You should discuss with your doctor the most important side effects of this drug prior to your using it. **ALWAYS FEEL FREE TO CONTACT YOUR DOCTOR WITH ANY QUESTIONS OR CONCERNS YOU MAY HAVE ABOUT FENTANYL TRANSDERMAL SYSTEM AND ANY SUSPECTED SIDE EFFECTS.**

SOME OF THE IMPORTANT THINGS TO HELP YOU USE THIS MEDICATION PROPERLY INCLUDE:

- (1) One important side effect is slow, shallow, and/or difficulty in breathing, which can occur if the dose of fentanyl transdermal system is too high. You and your household members should discuss with your doctor what signs and symptoms to look for and what to do if these develop. If you are uncertain what to do, call your doctor or get other emergency medical help.
- (2) Do not take other medications (prescriptions or over-the-counter) while wearing fentanyl transdermal system unless specifically told to do so by your doctor. Be especially careful about drugs that can make you sleepy.
- (3) Do not drink alcohol while wearing the patch. Also do not drive a vehicle or operate dangerous machinery unless specifically told that you may do so by your doctor.

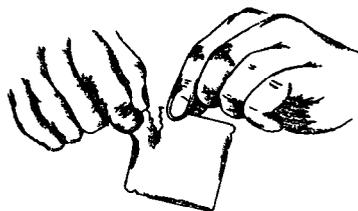
- (4) Direct sources of heat may increase the amount of medication you receive through the skin from the patch. Do not use electric blankets, heating pads, sun lamps, heated water beds, or other sources of direct heat on a patch. Avoid sun bathing, long hot baths, or other sources of heat to the body.
- (5) If you develop a fever greater than 102°F, contact your doctor because the increased fever could cause you to receive more medication than you should from the patch.
- (6) Do not wear more than one patch at a time unless specifically told to do so by your doctor.
- (7) Do not use this patch if you are nursing an infant unless specifically told to do so by your doctor. The medication can get into human milk and can cause serious problems for the infant.
- (8) Fentanyl transdermal system should not be used by children less than 12 years old or patients less than 18 years old who weigh less than 110 pounds, unless your doctor has enrolled the patient in an authorized research program.
- (9) Be sure to dispose of used and unused patches so they cannot be touched by any other people or pets.

How and Where to Apply Fentanyl Transdermal System

In the hospital, your doctor or another qualified 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.

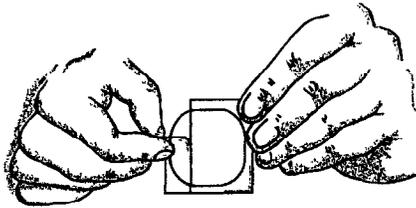
Step 1

Each fentanyl transdermal system is sealed in its own protective pouch. Until you are ready to use fentanyl transdermal system, do not remove it from the pouch. When you are ready to put on fentanyl transdermal system, tear open the pouch and remove the fentanyl transdermal system patch.



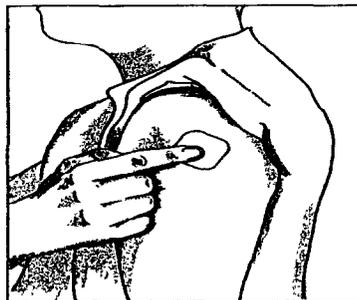
Step 2

Slide away the unattached oversized, clear protective films (top and bottom) from the patch and throw away. A clear oversized protective liner covers the sticky side of the fentanyl transdermal system – the side that will be put on your skin. Remove the clear plastic protective liner from the patch by gently peeling off one half of the protective liner at a time as shown in the drawing below. Try to avoid touching the sticky side of the fentanyl transdermal system. Throw away the liner.



Step 3

Immediately after you have taken fentanyl transdermal system from the pouch, apply the sticky side of the fentanyl transdermal system to a non-hairy, dry area of your chest, back, flank or upper arm. If the area you select has body hair, clip (do not shave) the hair close to the skin with scissors. Do not put fentanyl transdermal system on skin that is excessively oily, burned, broken out, cut, irritated or damaged in any way. If you need to clean the skin where the patch will be applied, use only clear water. Do not use soaps, oils, lotions, alcohol or other products that might irritate the skin under the patch. Make sure that the skin is completely dry. **Press the fentanyl transdermal system firmly on your skin with the palm of your hand for about 30 seconds.** Make sure it sticks well to your skin, especially around the edges of the patch.



Not all adhesive products stick to all patients. If the patch does not stick well or loosens after application, tape the edges down with first aid tape. In the event that the patch falls off, discard it and put a new one on at a different skin site (see **Disposing of Fentanyl Transdermal System**).

Step 4

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

Step 5

After wearing Fentanyl Transdermal System for three days, remove it (see **Disposing of Fentanyl Transdermal System**). Then choose a *different* place on your skin to apply a new fentanyl transdermal system and repeat Steps 1 to 4, in order.

When to Apply Fentanyl Transdermal System

If you need continued pain control, wear fentanyl transdermal system continuously for three days (approximately 72 hours), or as directed by your doctor and then remove the patch and replace it as directed by your doctor. Do not apply the new fentanyl transdermal system to the same place where you removed the last fentanyl transdermal system.

Your doctor may increase your fentanyl transdermal system dose if your pain is not adequately controlled. **IF YOU CONTINUE TO HAVE PAIN CALL YOUR DOCTOR.**

Water and Fentanyl Transdermal System

You can bathe, swim or shower while you are wearing fentanyl transdermal system. If the patch does fall off, put a new fentanyl transdermal system on your skin. Before putting on a new fentanyl transdermal system, make sure the new skin area you have selected is dry.

Disposing of Fentanyl Transdermal System

Before putting on a new fentanyl transdermal system, remove the patch you have been wearing. Fold the used fentanyl transdermal system in half so that the sticky side sticks to itself. Flush the used fentanyl transdermal system down the toilet immediately. Even used fentanyl transdermal system patches contain enough fentanyl to poison infants, 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 and flush the patch down the toilet. Do not flush the pouch or the protective liner.

Safety and Handling

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

The patch must be used only on the skin of the person for whom it was prescribed. If the patch dislodges and accidentally adheres to the skin of another person, take the patch off immediately and call a doctor.

Storage Instructions

Keep fentanyl transdermal system in its protective pouch until you are ready to use it.

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

Do not store unpouched or above 77°F (25°C). Remember, the inside of your car can reach temperatures much higher than this in the summer. Do not refrigerate.

Revised October 2002