CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

76-258

Generic Name:	Fentanyl Transdermal System 25mcg/hr, 50mcg/hr, 75mcg/hr, and 100mcg/hr
Sponsor:	Mylan Technologies, Inc.
Approval Date:	November 21, 2003

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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Reviews / Information Included in this ANDA Review.

Approval Letter(s)	X
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CSO Labeling Review(s)	X
Medical Officer Review(s)	X
Chemistry Review(s)	X
Microbiology Review(s)	X
Bioequivalence Review(s)	X
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Correspondence	X

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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APPROVAL LETTER

ANDA 76-258

NOV 21 2003

Mylan Technologies, Inc.
Attention: William Brochu
110 Lake Street
St. Albans, VT 05478

Dear Sir:

This is in reference to your abbreviated new drug application dated October 12, 2001, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (Act), for Fentanyl Transdermal System, 25 mcg/hr, 50 mcg/hr, 75 mcg/hr and 100 mcg/hr.

Reference is also made to your amendments dated October 14, 2002; April 5, June 27, October 24 and November 20, 2003.

Your application contains a patent certification to patent 4588580 under Section 505(j)(2)(A)(vii)(IV) of the Act. Section 505(j)(5)(B)(iii) of the Act provides that approval shall be made effective immediately unless an action is brought for infringement of the patent which is the subject of the certification before the expiration of forty-five days from the date the notice provided under paragraph (2)(B)(i) is received. You have notified FDA that Mylan Technologies, Inc. has complied with the requirements of Section 505(j)(2)(B) of the Act. No action for patent infringement was brought against Mylan Technologies, Inc. within the statutory forty-five day period.

The listed drug product (RLD) referenced in your application, Duragesic® of Alza Corporation, is subject to a period of exclusivity related to their recently approved pediatric labeling. As noted in the agency's publication entitled Approved Drug Products with Therapeutic Equivalence Evaluations, the Orange Book, Alza Corporation is entitled to a period of exclusivity for certain revisions made to the approved package insert labeling for Duragesic®. This exclusivity is scheduled to expire on November 20, 2006. Section 11 of the Best Pharmaceuticals for Children Act (BPCA), signed into law in January 2002, allows certain portions of the labeling for Duragesic® which is subject to pediatric exclusivity protection

to be omitted from the labeling of products approved under section 505(j) of the Act. The BPCA also permits the incorporation of language in the labeling of products approved under section 505(j) that informs health care practitioners that Duragesic® has been approved for pediatric use. The agency has determined that the final printed labeling you have submitted is in compliance with the BPCA with respect to pediatric use protected by exclusivity.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Fentanyl Transdermal System, 25 mcg/hr, 50 mcg/hr, 75 mcg/hr and 100 mcg/hr to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Duragesic®, 0.6 mg/24 hr, 1.2 mg/24 hr, 1.8 mg/24 hr and 2.4 mg/24 hr respectively, of Alza Corporation). Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application. The "interim" dissolution specifications are as follows:

The dissolution testing should be conducted in [redacted] using USP Apparatus [redacted] rpm. The test product should meet the following specifications:

0.5 Hr: [redacted]
1 Hr: [redacted]
2 Hrs: [redacted]
8 Hrs: NLT [redacted]

The "interim" dissolution test(s) and tolerances should be finalized by submitting dissolution data for the first three production size batches. Data should be submitted as a "Special Supplement - Changes Being Effected" when there are no revisions to the "interim" specifications or when the final specifications are tighter than the "interim" specifications. In all other instances, the information should be submitted in the form of a Prior Approval Supplement.

With respect to 180-day generic drug exclusivity, we note that Mylan Technologies, Inc. was the first to submit a substantially complete ANDA with a Paragraph IV Certification. Therefore, with this approval Mylan Technologies, Inc. is eligible for 180-days of market exclusivity. Such exclusivity will begin to run either from the date Mylan Technologies, Inc. Begins commercial marketing of the drug product, or in the absence of marketing, from the date of a decision of a court finding the patent invalid or not infringed whichever event occurs earlier [Section 505(j)(5)(B)(iv)].

With respect to the "first commercial marketing" trigger for the commencement of exclusivity, please refer to 21 CFR 314.107(c)(4). The Agency expects that you will begin commercial marketing of this drug product in a prompt manner. Please submit correspondence to your application stating the date you commence commercial marketing of this product, or the date of a decision of the court holding the relevant patent invalid, unenforceable or not infringed.

If you have any questions concerning the effective date of approval of an abbreviated new drug application and the Agency's elimination of the requirement that an ANDA applicant successfully defend a patent infringement suit to be eligible for 180-days of marketing exclusivity, please refer to the interim rule published in the November 5, 1998 Federal Register (Volume 63, No. 214, 59710).

Under Section 506A of the Act, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-40). Please do not use Form FDA 2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-40) with a completed Form FDA 2253 at the time of their initial use.

Sincerely yours,

Gary Buehler 11/21/03
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

76-258

FINAL PRINTED LABELING

76-258

"SPECIMEN"

FTS:R3

FENTANYL TRANSDERMAL SYSTEM

FENTANYL TRANSDERMAL SYSTEM

℞ only

C II

Full Prescribing Information

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

- **In the management of acute or postoperative 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.)

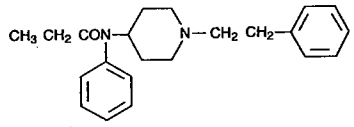
SAFETY OF FENTANYL TRANSDERMAL SYSTEM HAS NOT BEEN ESTABLISHED IN CHILDREN UNDER 2 YEARS OF AGE. FENTANYL TRANSDERMAL SYSTEM SHOULD BE ADMINISTERED TO CHILDREN ONLY IF THEY ARE OPIOID-TOLERANT AND AGE 2 YEARS OR OLDER (see PRECAUTIONS: Pediatric Use).

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

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

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

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



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

System Components and Structure: The amount of fentanyl released from each system per hour is proportional to the surface area (25 mcg/hr per 6.25 cm^2). The composition per unit area of all system sizes is identical.

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

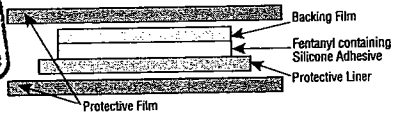
*Nominal delivery rate per hour
**FOR USE ONLY IN OPIOID TOLERANT PATIENTS

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.

(Diagram Not to Scale)



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APPROVED

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

Do not use cut or damaged fentanyl transdermal systems.

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

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

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

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

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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 (25, 50, 75, and 100 mcg of fentanyl per hour) is 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

"SPECIMEN"

FTS:R3

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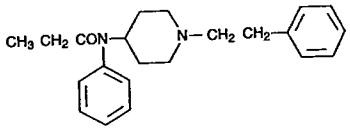

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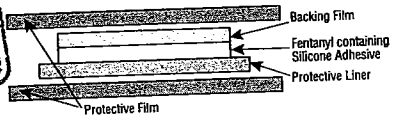

NOV 21 2003
APPROVED

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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)

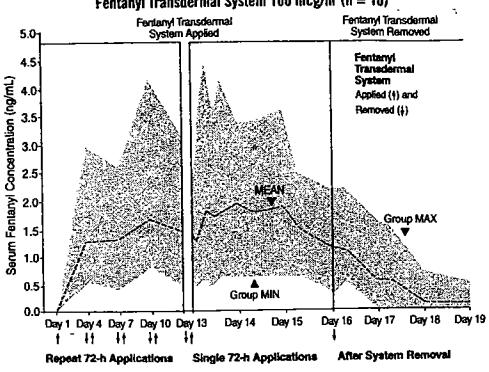


TABLE A
FENTANYL PHARMACOKINETIC PARAMETERS FOLLOWING FIRST 72-HOUR APPLICATION OF FENTANYL TRANSDERMAL SYSTEM

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).

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

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

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

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

Pharmacodynamics: Analgesia: Fentanyl transdermal system is a strong opioid analgesic. In controlled clinical trials in non-opioid-tolerant patients, 60 mg/day IM morphine was considered to provide analgesia approximately equivalent to fentanyl transdermal system 100 mcg/hr in an acute pain model.

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

Ventilatory Effects: At equivalent analgesic serum concentrations, fentanyl and morphine produce a similar degree of hypoventilation. A small number of patients have experienced clinically significant hypoventilation with fentanyl transdermal system. Hypoventilation was manifested by respiratory rates of less than 8 breaths/minute or a pCO_2 greater than 55 mm Hg. In clinical trials of 357 postoperative (acute pain) patients treated with fentanyl transdermal system, 13 patients experienced hypoventilation. In these studies the incidence of hypoventilation was higher in nontolerant women (10) than in men (3) and in patients weighing less than 63 kg (9 of 13). Although patients with impaired respiration were not common in the trials, they had higher rates of hypoventilation. In addition, postmarketing reports have been received of opioid-naive 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 in adults exceeding 25 mcg/hr is contraindicated in patients who are not tolerant to opioid therapy. A fentanyl transdermal system should only be administered to children if they are opioid-tolerant and age 2 years or older.

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

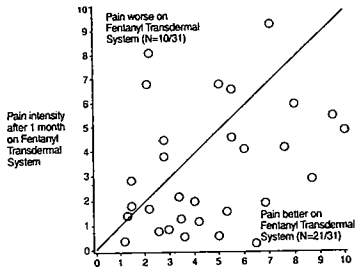
See BOX WARNING, CONTRAINDICATIONS, WARNINGS, PRECAUTIONS, ADVERSE REACTIONS and OVERDOSAGE for additional information on hypoventilation.

Cardiovascular Effects: Fentanyl may infrequently produce bradycardia. The incidence of bradycardia in clinical trials with fentanyl transdermal system was less than 1%.

CNS Effects: IN OPIOID NAIVE PATIENTS, CENTRAL NERVOUS SYSTEM EFFECTS INCREASE WHEN SERUM FENTANYL CONCENTRATIONS ARE GREATER THAN 3 NG/ML.

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).

Visual Analogue Score of Pain Intensity Ratings at Entry in the Study and After One Month of Fentanyl Transdermal System Use



Pain Intensity on Pre-Study Analgesic Regimen

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

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

Fentanyl transdermal system should not be used in the management of acute or postoperative pain because serious or life-threatening hypoventilation could result. (See BOX WARNING and CONTRAINDICATIONS.)

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

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

- **In the management of acute or postoperative pain, including use in outpatient 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.

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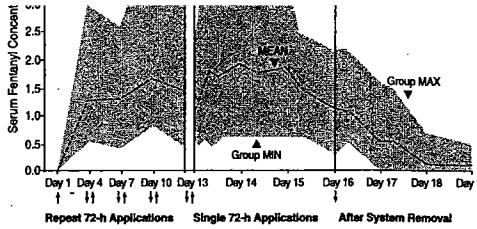


TABLE A
FENTANYL PHARMACOKINETIC PARAMETERS FOLLOWING FIRST 72-HOUR APPLICATION OF FENTANYL TRANSDERMAL SYSTEM

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).

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

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

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

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

Pharmacodynamics: Analgesia: Fentanyl transdermal system is a strong opioid analgesic. In controlled clinical trials in non-opioid-tolerant patients, 60 mg/day IM morphine was considered to provide analgesia approximately equivalent to fentanyl transdermal system 100 mcg/hr in an acute pain model.

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

Ventilatory Effects: At equivalent analgesic serum concentrations, fentanyl and morphine produce a similar degree of hypoventilation. A small number of patients have experienced clinically significant hypoventilation with fentanyl transdermal system. Hypoventilation was manifested by respiratory rates of less than 8 breaths/minute or a pCO_2 greater than 55 mm Hg. In clinical trials of 357 postoperative (acute pain) patients treated with fentanyl transdermal system, 13 patients experienced hypoventilation. In these studies the incidence of hypoventilation was higher in nontolerant women (10) than in men (3) and in patients weighing less than 63 kg (9 of 13). Although patients with impaired respiration were not common in the trials, they had higher rates of hypoventilation. In addition, postmarketing reports have been received of opioid-naive 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 in adults exceeding 25 mcg/hr is contraindicated in patients who are not tolerant to opioid therapy. A fentanyl transdermal system should only be administered to children if they are opioid-tolerant and age 2 years or older.

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

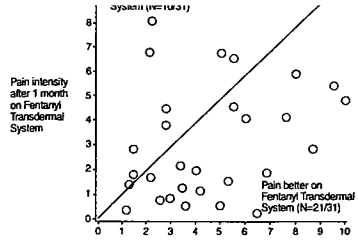
See BOX WARNING, CONTRAINDICATIONS, WARNINGS, PRECAUTIONS, ADVERSE REACTIONS and OVERDOSAGE for additional information on hypoventilation.

Cardiovascular Effects: Fentanyl may infrequently produce bradycardia. The incidence of bradycardia in clinical trials with fentanyl transdermal system was less than 1%.

CNS Effects: IN OPIOID NAIVE PATIENTS, CENTRAL NERVOUS SYSTEM EFFECTS INCREASE WHEN SERUM FENTANYL CONCENTRATIONS ARE GREATER THAN 3 NG/ML.

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

The analgesic efficacy of fentanyl transdermal system was demonstrated in an acute pain model with surgical procedures expected to produce various intensities of pain (e.g., hysterectomy, major orthopedic surgery). Clinical use and safety was evaluated in patients experiencing chronic pain due to malignancy. Based on the results of these trials, 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.)



Pain Intensity on Pre-Study Analgesic Regimen

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

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

Fentanyl transdermal system should not be used in the management of acute or postoperative pain because serious or life-threatening hypoventilation could result. (See BOX WARNING and CONTRAINDICATIONS.)

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

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

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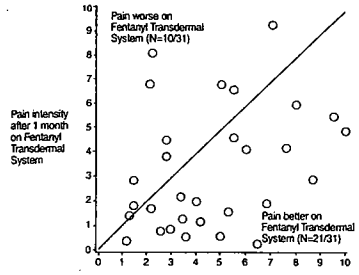
Drug Interactions: ***Central Nervous System Depressants:*** When patients are receiving fentanyl transdermal system, the dose of additional opioids or other CNS depressant drugs (including benzodiazepines) should be reduced by at least 50%. With the concomitant use of CNS depressants, hypotension may 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 adjustment made if warranted.

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).

Visual Analogue Score of Pain Intensity Ratings at Entry in the Study and After One Month of Fentanyl Transdermal System Use



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

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

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

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

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

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

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

Pediatric Use: Fentanyl transdermal system was not studied in children under 2 years of age. Fentanyl transdermal system should be administered to children only if they are opioid tolerant and age 2 years or older (see DOSAGE AND ADMINISTRATION and BOX WARNING).

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

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

Since elderly, cachectic, or debilitated patients may have altered pharmacokinetics due to poor fat stores, muscle wasting, or altered clearance, they should not be started on fentanyl transdermal system doses higher than 25 mcg/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 system dispensed to the patient.

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

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

Pre-Marketing Clinical Trial Experience:

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

HYPOVENTILATION WAS THE MOST SERIOUS ADVERSE REACTION OBSERVED IN 13 (4%) POSTOPERATIVE PATIENTS AND IN 3 (2%) OF THE CANCER PATIENTS. HYPOTENSION AND HYPERTENSION WERE OBSERVED IN 11 (3%) AND 4 (1%) OF THE OPIOID-NAIVE PATIENTS.

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

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

In the pediatric population, the safety of fentanyl transdermal system has been evaluated in 291 patients ages 2 to 18 years with chronic pain. The duration of fentanyl transdermal system used varied; 20% of pediatric patients were treated for ≤ 15 days; 46% for 16 to 30 days; 16% for 31 to 60 days; and 17% for at least 61 days. Twenty-five patients were treated with fentanyl transdermal system for at least 4 months and 9 patients for more than 9 months. There was no apparent pediatric-specific risk associated with fentanyl transdermal system use in children as young as 2 years old when used as directed.

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

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

TABLE 1: ADVERSE EVENTS (at rate of ≥ 1%)
Adults (N=153) and Pediatric (N=291) Pre-Marketing Clinical Trial Experience

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

*Reactions occurring in 3% to 10% of fentanyl transdermal system patients
**Reactions occurring in 10% or more of fentanyl transdermal system patients

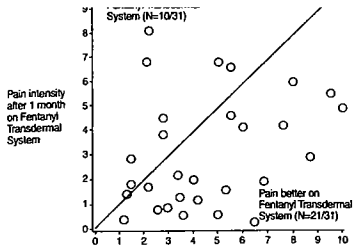
The following adverse effects have been reported in less than 1% of the 510 adult postoperative and cancer patients studied; the association between these events and fentanyl transdermal system administration is unknown. This information is listed to serve as alerting information for the physician.

Cardiovascular: bradycardia

Digestive: abdominal distention

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

Respiratory: stertorous breathing, asthma, respiratory disorder



Pain Intensity on Pre-Study Analgesic Regimen

iatrics: The safety of fentanyl transdermal system was evaluated in three open-label trials in 291 pediatric ents, 2 years through 18 years of age, with chronic pain. Starting doses of 25 mcg/hr and higher were used by patients. Approximately 90% of the total daily opioid requirement (fentanyl transdermal system plus rescue lication) was provided by fentanyl transdermal system.

ICATIONS AND USAGE: Fentanyl transdermal system is indicated in the management of chronic pain in patients require continuous opioid analgesia for pain that cannot be managed by lesser means such as acetaminophen-iid 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 ous 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 mini-e the risk of adverse effects while providing analgesia. In properly selected patients, fentanyl transdermal sys- is a safe and effective alternative to other opioid regimens. (See DOSAGE AND ADMINISTRATION.)

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

- **In the management of acute or postoperative pain, including use in outpatient 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 adhe-es.

RNINGS: The safety of fentanyl transdermal system has not been established in children under 2 years of . A FENTANYL TRANSDERMAL SYSTEM SHOULD BE ADMINISTERED TO CHILDREN ONLY IF THEY ARE OPIOID-TOL-ANT AND AGE 2 YEARS OR OLDER (see PRECAUTIONS: Pediatric Use).

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

FENTANYL TRANSDERMAL SYSTEM SHOULD BE PRESCRIBED ONLY BY PERSONS KNOWLEDGEABLE IN THE CON-UOUS ADMINISTRATION OF POTENT OPIOIDS, IN THE MANAGEMENT OF PATIENTS RECEIVING POTENT OPIOIDS FOR EATMENT OF PAIN, AND IN THE DETECTION AND MANAGEMENT OF HYPOVENTILATION INCLUDING THE USE OF OPI-I ANTAGONISTS.

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

ALL PATIENTS AND THEIR CAREGIVERS SHOULD BE ADVISED TO AVOID EXPOSING THE FENTANYL TRANSDERMAL STEM APPLICATION SITE TO DIRECT EXTERNAL HEAT SOURCES, SUCH AS HEATING PADS OR ELECTRIC BLANKETS, AT LAMPS, SAUNAS, HOT TUBS, AND HEATED WATER BEDS, ETC., WHILE WEARING THE SYSTEM. THERE IS A POTEN-L FOR TEMPERATURE-DEPENDENT INCREASES IN FENTANYL RELEASE FROM THE SYSTEM. (See PRECAUTIONS: ients with Fever/External Heat.)

ECAUTIONS: General: Fentanyl transdermal system doses greater than 25 mcg/hr are too high for initiation of rapy in non-opioid-tolerant patients and should not be used to begin fentanyl transdermal system therapy in se patients. Children converting to fentanyl transdermal system should be opioid-tolerant (see BOX WARNING).

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

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

poventilation (Respiratory Depression): Hypoventilation may occur at any time during the use of fentanyl trans-rmal system. Because significant amounts of fentanyl are absorbed from the skin for 17 hours or more after the stem is removed, hypoventilation may persist beyond the removal of fentanyl transdermal system. Consequently, tients with hypoventilation should be carefully observed for degree of sedation and their respiratory rate moni-ed until respiration has stabilized.

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

ronic Pulmonary Disease: Because potent opioids can cause hypoventilation, fentanyl transdermal system should be ministered with caution to patients with pre-existing medical conditions predisposing them to hypoventilation. In such tients, normal analgesic doses of opioids may further decrease respiratory drive to the point of respiratory failure.

ad Injuries and Increased Intracranial Pressure: Fentanyl transdermal system should not be used in patients o may be particularly susceptible to the intracranial effects of CO_2 retention such as those with evidence of in-eased intracranial pressure, impaired consciousness, or coma. Opioids may obscure the clinical course of patients th head injury. Fentanyl transdermal system should be used with caution in patients with brain tumors.

rdiac Disease: FENTANYL MAY PRODUCE BRADYCARDIA. FENTANYL SHOULD BE ADMINISTERED WITH CAUTION TO TIENTS WITH BRADYARRHYTHMIAS.

patic or Renal Disease: At the present time insufficient information exists to make recommendations regarding e use of fentanyl transdermal system in patients with impaired renal or hepatic function. If the drug is used in ese patients, it should be used with caution because of the hepatic metabolism and renal excretion of fentanyl.

tients with Fever/External Heat: Based on a pharmacokinetic model, serum fentanyl concentrations could theo-tically increase by approximately one third for patients with a body temperature of 40°C (104°F) due to tempera-re-dependent increases in fentanyl release from the system and increased skin permeability. Therefore, patients earing fentanyl transdermal system who develop fever should be monitored for opioid side effects and the fenta-l transdermal system dose should be adjusted if necessary.

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ug Interactions: ***Central Nervous System Depressants:*** When patients are receiving fentanyl transdermal sys m, the dose of additional opioids or other CNS depressant drugs (including benzodiazepines) should be reduce at least 50%. With the concomitant use of CNS depressants, hypotension may occur.

gents Affecting Cytochrome P450 3A4 Isoenzyme System: CYP3A4 Inhibitors: Since the metabolism of fentanyl mediated by the CYP3A4 isozyme, coadministration of drugs that inhibit CYP3A4 activity may cause decrease earance of fentanyl. The expected clinical results would be increased or prolonged opioid effects. Thus patient administered with inhibitors of CYP3A4 such as macrolide antibiotics (e.g., erythromycin), azole antifungal agen .g., ketoconazole), and protease inhibitors (e.g., ritonavir) while receiving fentanyl transdermal system should refully monitored and dosage adjustment made if warranted.

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

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

Post-Marketing Experience: Adults: The following adverse reactions reported to have been observed in association with the use of fentanyl transdermal system and not reported in the pre-marketing adverse reactions section above include:
Body as a Whole: edema
Cardiovascular: tachycardia
Metabolic and Nutritional: weight loss
Special Senses: blurred vision

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

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

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

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

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

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

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

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

Fentanyl transdermal system should be applied immediately upon removal from the sealed package. Do not alter the system (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. Pediatric patients converting to fentanyl transdermal system with a 25 mcg/hr patch should be opioid-tolerant and receiving at least 45 mg oral morphine equivalents per day. The dose-conversion schedule described in Table C and method of titration described below were used safely in opioid-tolerant pediatric patients over the age of 2 years with chronic pain (see PRECAUTIONS: Pediatric Use).

In selecting an initial fentanyl transdermal system dose, attention should be given to 1) the daily dose, potency, and characteristics of the opioid the patient has been taking previously (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, 25 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. 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]	Equianalgesic Dose (mg) PO
Morphine	10	60 (30)[d]
Hydromorphone (Dilaudid®)[1]	1.5	7.5
Methadone (Dolophine®)[2]	10	20
Oxycodone	15	30
Levorphanol (Levo-Dromoran®)[3]	2	4
Oxymorphone (Numorphan®)[4]	1	10 (PR)
Meperidine (Demerol®)[5]	75	—
Codeine	130	200

[a]All IM and PO doses in this chart are considered equivalent to 10 mg of IM morphine in analgesic effect. IM denotes intramuscular, PO oral, and PR rectal.
[b]Based on single-dose studies in which an intramuscular dose of each drug listed was compared with morphine to establish the relative potency. Oral doses are those recommended when changing from parenteral to an oral route. Reference: Foley, K.M. (1985) The treatment of cancer pain. NEJM 313(2):84-95.
[c]Although controlled studies are not available, in clinical practice it is customary to consider the doses of opioid given IM, IV or subcutaneously to be equivalent. There may be some differences in pharmacokinetic parameters such as C_{max} and T_{max}.
[d]The conversion ratio of 10 mg parenteral morphine = 30 mg oral morphine is based on clinical experience in patients with chronic pain. The conversion ratio of 10 mg parenteral morphine = 60 mg oral morphine is based on a potency study in acute pain. Reference: Ashburn and Lipman (1993) Management of pain in the cancer patient. Anesth Analg 76:402-416.

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[5]Demerol® is a registered trademark of SANOFI-SYNTHELABO INC.

TABLE D[1]
RECOMMENDED INITIAL FENTANYL TRANSDERMAL SYSTEM DOSE BASED UPON DAILY ORAL MORPHINE DOSE

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

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

[1]THIS TABLE SHOULD NOT BE USED TO CONVERT FROM FENTANYL TRANSDERMAL SYSTEM TO OTHER THERAPIES, BECAUSE THIS CONVERSION TO FENTANYL TRANSDERMAL SYSTEM IS CONSERVATIVE. USE OF TABLE D FOR CONVERSION TO OTHER ANALGESIC THERAPIES CAN OVERESTIMATE THE DOSE OF THE NEW AGENT. OVERDOSAGE OF THE NEW ANALGESIC AGENT IS POSSIBLE. (SEE DOSAGE AND ADMINISTRATION: DISCONTINUATION OF FENTANYL TRANSDERMAL SYSTEM.)
[2]PEDIATRIC PATIENTS INITIATING THERAPY ON A 25 MCG/HR FENTANYL TRANSDERMAL SYSTEM SHOULD BE OPIOID-TOLERANT AND RECEIVING AT LEAST 45 MG ORAL MORPHINE EQUIVALENTS PER DAY.

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

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

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

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

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

Appropriate dosage increments should be based on the daily dose of supplementary opioids, using the ratio of 90 mg/24 hours of oral morphine to a 25 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 at what dose level the opioid may be discontinued without producing the signs and symptoms of abrupt withdrawal.

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

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

Fentanyl Transdermal System Dose (mcg/hr)	System Size (cm^2)	Fentanyl Content (mg)	NDC Number
Fentanyl Transdermal System –25	6.25	2.55	0378-9121-98
Fentanyl Transdermal System –50*	12.5	5.10	0378-9122-98
Fentanyl Transdermal System –75*	18.75	7.65	0378-9123-98
Fentanyl Transdermal System –100*	25	10.20	0378-9124-98

* FOR USE ONLY IN OPIOID TOLERANT PATIENTS

Safety and Handling: Fentanyl transdermal system is supplied in sealed transdermal systems which pose little risk of exposure to health care workers. 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 above 77°F (25°C). 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.

MYLAN®

Mylan Pharmaceutical Inc.
Morgantown, WV 26505

REVISED NOVEMBER 2003
FTS:R3

Patient Information
FENTANYL TRANSDERMAL SYSTEM

CII

℞ only

This leaflet contains important information about fentanyl transdermal system. Read this patient information carefully before you start using fentanyl transdermal system. Read it each time you get a prescription. There may be new information. This information does not take the place of talking to your health care provider about your medical condition or your treatment. Only your health care provider can decide if fentanyl transdermal system is the right treatment for you. If you do not understand some of this information or have questions, talk with your health care provider.

What is the most important information I should know about fentanyl transdermal system?

- **Only use fentanyl transdermal system the way your health care provider recommends.**
- **Fentanyl transdermal system contains fentanyl, a narcotic pain medicine that if taken the wrong way can lead to serious problems, including overdose and death.**
- **Fentanyl transdermal system should only be used to treat chronic (continuing) pain that is moderate to severe.**
  - When strong pain medicines are needed, and
  - When pain medicine is needed around the clock (all the time)
- **Fentanyl transdermal system should not be used to treat pain that will last only a few days.** This includes the pain that happens with surgery, medical, or dental procedures.
- **Fentanyl transdermal system should only be used in children age 2 years or older who are already using other narcotic pain medicines (opioid tolerant).** Fentanyl transdermal system has not been studied in children who are less than 2 years of age. It is not known if fentanyl transdermal system would be safe in these

tration of a specific narcotic antagonist such as naloxone. The duration of hypoventilation following an overdose may be longer than the effects of the narcotic antagonist's action (the half-life of naloxone ranges from 30 to 81 minutes). The interval between IV antagonist doses should be carefully chosen because of the possibility of re-narcotization after system removal; repeated administration of naloxone may be necessary. Reversal of the narcotic effect may result in acute onset of pain and the release of catecholamines.

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

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

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

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

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

Fentanyl transdermal system should be applied immediately upon removal from the sealed package. Do not alter the system (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. Pediatric patients converting to fentanyl transdermal system with a 25 mcg/hr patch should be opioid-tolerant and receiving at least 45 mg oral morphine equivalents per day. The dose-conversion schedule described in Table C and method of titration described below were used safely in opioid-tolerant pediatric patients over the age of 2 years with chronic pain (see PRECAUTIONS: Pediatric Use).

In selecting an initial fentanyl transdermal system dose, attention should be given to 1) the daily dose, potency, and characteristics of the opioid the patient has been taking previously (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, 25 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. 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]	1.5	7.5
Methadone (Dolophine®)[2]	10	20
Oxycodone	15	30
Levorphanol (Levo-Dromoran®)[3]	2	4
Oxymorphone (Numorphan®)[4]	1	10 (PR)
Meperidine (Demerol®)[5]	75	—
Codeine	130	200

[a] All IM and PO doses in this chart are considered equivalent to 10 mg of IM morphine in analgesic effect. IM denotes intramuscular, PO oral, and PR rectal.
[b] Based on single-dose studies in which an intramuscular dose of each drug listed was compared with morphine to establish the relative potency. Oral doses are those recommended when changing from parenteral to an oral route. Reference: Foley, K.M. (1985) The treatment of cancer pain. NEJM 313(2):84-95.
[c] Although controlled studies are not available, in clinical practice it is customary to consider the doses of opioid given IM, IV or subcutaneously to be equivalent. There may be some differences in pharmacokinetic parameters such as C_{max} and T_{max}.
[d] The conversion ratio of 10 mg parenteral morphine = 30 mg oral morphine is based on clinical experience in patients with chronic pain. The conversion ratio of 10 mg parenteral morphine = 60 mg oral morphine is based on a potency study in acute pain. Reference: Ashburn and Lipman (1993) Management of pain in the cancer patient. Anesth Analg 76:402-416.

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45 to 134[2]	25
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495 to 584	150
585 to 674	175
675 to 764	200
765 to 854	225
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945 to 1034	275
1035 to 1124	300

continued

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

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

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

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

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

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

Appropriate dosage increments should be based on the daily dose of supplementary opioids, using the ratio of 90 mg/24 hours of oral morphine to a 25 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 at what dose level the opioid may be discontinued without producing the signs and symptoms of abrupt withdrawal.

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Fentanyl Transdermal System –50*	12.5	5.10	0378-9122-98
Fentanyl Transdermal System –75*	18.75	7.65	0378-9123-98
Fentanyl Transdermal System –100*	25	10.20	0378-9124-98

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

Do not store above 77°F (25°C). 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.

MYLAN®

Mylan Pharmaceutical Inc.
Morgantown, WV 26505

REVISED NOVEMBER 2003
FTS:R3

Patient Information
FENTANYL TRANSDERMAL SYSTEM

CII

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This leaflet contains important information about fentanyl transdermal system. Read this patient information carefully before you start using fentanyl transdermal system. Read it each time you get a prescription. There may be new information. This information does not take the place of talking to your health care provider about your medical condition or your treatment. Only your health care provider can decide if fentanyl transdermal system is the right treatment for you. If you do not understand some of this information or have questions, talk with your health care provider.

What is the most important information I should know about fentanyl transdermal system?

- **Only use fentanyl transdermal system the way your health care provider recommends.**
- **Fentanyl transdermal system contains fentanyl, a narcotic pain medicine that if taken the wrong way can lead to serious problems, including overdose and death.**
- **Fentanyl transdermal system should only be used to treat chronic (continuing) pain that is moderate to severe.**
  - When strong pain medicines are needed, and
  - When pain medicine is needed around the clock (all the time)
- **Fentanyl transdermal system should not be used to treat pain that will last only a few days.** This includes the pain that happens with surgery, medical, or dental procedures.
- **Fentanyl transdermal system should only be used in children age 2 years or older who are already using other narcotic pain medicines (opioid tolerant).** Fentanyl transdermal system has not been studied in children who are less than 2 years of age. It is not known if fentanyl transdermal system would be safe in these children.
- **Only use fentanyl transdermal system for the condition for which it was prescribed.**

What is fentanyl transdermal system?

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

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

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

...re pregnant or planning to become pregnant. Fentanyl transdermal system may harm your unborn baby.

...re breast feeding. The medicine in fentanyl transdermal system passes into your milk and can harm your ...aby.

...ave trouble breathing or lung problems
...ve a head injury or brain problems
...ve a heart problem called bradycardia (slow heart beat)
...ve liver problems
...ve kidney problems
...ve a history of drug or alcohol abuse
...ve skin reactions to adhesives (glues) used in fentanyl transdermal system. See the end of this leaflet ...a complete list of all the ingredients in fentanyl transdermal system.

...dicines may cause serious side effects when used with fentanyl transdermal system. Tell your health ...ider about all the medicines you take including prescription and non-prescription medicines, vitamins, ...l supplements. Sometimes, the doses of certain medicines and fentanyl transdermal system need to be ...hen used together.

...ld I know about using fentanyl transdermal system in children?

...anyl transdermal system can be used in children 2 years or older only if they are opioid-tolerant. These are ...dren who are using other narcotic pain medicines for continuing pain right before starting fentanyl trans... ...al system.

...anyl transdermal system has not been studied in children who are less than 2 years old. It is not known if ...uld be safe in these children.

...ung children, put the patch on the upper back. This will lower the chances that the child will remove the ...h and put it in their mouth.

...this medicine in a safe place. Keep fentanyl transdermal system out of the reach of children.

...e fentanyl transdermal system?

...r your health care provider's directions exactly. Your health care provider may change your dose based ...ur reactions to the medicine. Do not change your dose or stop using fentanyl transdermal system unless ...ealth care provider tells you to. Do not use fentanyl transdermal system more often than prescribed. ...he end of this leaflet for "How and when to apply fentanyl transdermal system.")

...t wear more than **one** fentanyl transdermal system patch at a time, unless your health care provider ...ou to do so.

...ur health care provider right away if you get a fever higher than 102°F. A fever may cause too much of ...edicine in fentanyl transdermal system to pass into your body. Your health care provider may tell you to ...lower dose while you have a fever.

...se too much fentanyl transdermal system or overdose, get emergency medical help right away.

...ave concerns about addiction when using your pain medicine or if you have experienced drug or alco... ...fiction in the past, talk to your health care provider.

...u have stopped using a patch, be sure to fold the sticky sides of the patch together and flush it down ...et. Do not put used fentanyl transdermal system patches in a garbage can.

...ealth care provider tells you to stop using fentanyl transdermal system, throw away the unused pack... ...pen the unused packages and fold the sticky sides of the patches together, and flush them down the

...avoid while using fentanyl transdermal system?

...t use heat sources such as heating pads, electric blankets, heat lamps, saunas, hot tubs, or heat... ...terbeds. Do not take long hot baths or sun bathe. All of these can make your temperature rise and ...too much of the medicine in fentanyl transdermal system to pass into your body.

...t breast feed unless your health care provider tells you it is okay. Fentanyl transdermal system ...s into your milk and can cause serious problems for your baby.

...take other medicines without talking to your health care provider. Other medicines include pre... ...on and non-prescription medicines, vitamins, and herbal supplements. **Be especially careful about ...medicines that make you sleepy.**

...T DRINK ANY ALCOHOL WHILE USING FENTANYL TRANSDERMAL SYSTEM. IT CAN INCREASE YOUR ...ES OF HAVING DANGEROUS SIDE EFFECTS.

... DRIVE, OPERATE HEAVY MACHINERY, OR DO OTHER POSSIBLY DANGEROUS ACTIVITIES UNITL YOU ...OW FENTANYL TRANSDERMAL SYSTEM AFFECTS YOU. FENTANYL TRANSDERMAL SYSTEM CAN MAKE ...EEPY. ASK YOUR HEALTH CARE PROVIDER TO TELL YOU WHEN IT IS OKAY TO DO THESE ACTIVITIES.

... STOP USING FENTANYL TRANSDERMAL SYSTEM SUDDENLY. YOUR BODY CAN DEVELOP A PHYSICAL ...ENCE ON FENTANYL TRANSDERMAL SYSTEM. YOU CAN GET SICK IF YOU SUDDENLY STOP USING IT. ...YOUR HEALTH CARE PROVIDER ABOUT HOW TO SAFELY STOP USING FENTANYL TRANSDERMAL SYS...

...ssible side effects of fentanyl transdermal system?

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

- ...Slow breathing
- ...Shallow breathing (little chest movement with breathing)
- ...Trouble breathing

...h care provider right away or get emergency medical help if you have trouble breathing or have ...effects while using fentanyl transdermal system.

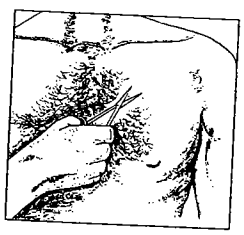
...ommon side effects with fentanyl transdermal system are nausea, vomiting, constipation, dry ...piness, confusion, weakness, and sweating. Although uncommon, trouble sleeping and seizures ...d in children. These are not all the possible side effects of fentanyl transdermal system. For a ...t, ask your health care provider or pharmacist.

...health care provider about any side effect that concerns you.

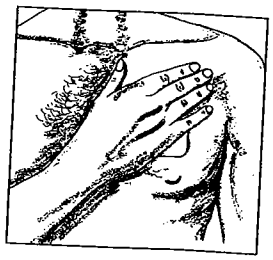
...apply fentanyl transdermal system

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

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



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



- Each fentanyl transdermal system patch is sealed in its own protective pouch. Do not remove the fentanyl transdermal system patch from the pouch until you are ready to use it. When you are ready to put on fentanyl transdermal system, tear open the pouch and remove the fentanyl transdermal system patch.
- Do not put the fentanyl transdermal system patch on skin that is very oily, burned, broken out, cut, irritated, or damaged in any way.
- If you have any questions about where on your body you should or should not apply the patch, please ask your health care provider.
- Fentanyl transdermal system may not stick to all patients. If the patch does not stick well or comes loose after applying, tape the edges down with first aid tape. If the patch falls off, throw it away and put a new one on at a different skin site (see "Disposing of fentanyl transdermal system").
- Wash your hands when you have finished applying fentanyl transdermal system.
- Remove fentanyl transdermal system after wearing it for 3 days (see "Disposing of fentanyl transdermal system"). Choose a *different* place on the skin to apply a new fentanyl transdermal system patch and repeat Steps 1 through 3. **Do not apply the new patch to the same place as the last one.**

When to apply fentanyl transdermal system

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

Water and fentanyl transdermal system

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

Disposing of fentanyl transdermal system

- BEFORE PUTTING ON A NEW FENTANYL TRANSDERMAL SYSTEM PATCH, REMOVE THE PATCH YOU HAVE BEEN WEARING.
- FOLD THE USED FENTANYL TRANSDERMAL SYSTEM PATCH IN HALF SO THAT THE STICKY SIDE STICKS TO ITSELF. **FLUSH THE USED FENTANYL TRANSDERMAL SYSTEM DOWN THE TOILET RIGHT AWAY. A USED FENTANYL TRANSDERMAL SYSTEM PATCH MAY BE DANGEROUS FOR OR EVEN LEAD TO DEATH IN BABIES, CHILDREN, PETS, AND ADULTS WHO HAVE NOT BEEN PRESCRIBED FENTANYL TRANSDERMAL SYSTEM.**
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Safety and handling of fentanyl transdermal system

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

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

How should fentanyl transdermal system be stored?

STORE FENTANYL TRANSDERMAL SYSTEM BELOW 77°F (25°C). REMEMBER, THE INSIDE OF YOUR CAR CAN REACH TEMPERATURES MUCH HIGHER THAN THIS IN THE SUMMER. DO NOT REFRIGERATE.

KEEP FENTANYL TRANSDERMAL SYSTEM IN ITS PROTECTIVE POUCH UNTIL YOU ARE READY TO USE IT.

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

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

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

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

FOR QUESTIONS ABOUT FENTANYL TRANSDERMAL SYSTEM CALL MYLAN PHARMACEUTICALS INC. PRODUCT INFORMATION AT 1-877 4 INFO-RX (1-877-446-3679) 8 A.M. TO 5 P.M. EST, MONDAY THROUGH FRIDAY.

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

WHAT ARE THE INGREDIENTS OF FENTANYL TRANSDERMAL SYSTEM?

ACTIVE INGREDIENT: FENTANYL

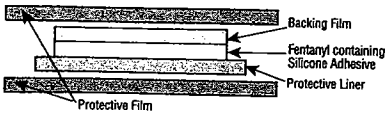
Inactive ingredients: Dimethicone NF, silicone adhesive and polyolefin film backing.

MYLAN®

Mylan Pharmaceuticals Inc.
Morgantown, WV 26505

REVISED NOVEMBER 2003
PL:FTS:R2

(Diagram Not to Scale)



Who should not use fentanyl transdermal system?

Do not use fentanyl transdermal system:

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

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

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

Some medicines may cause serious side effects when used with fentanyl transdermal system. Tell your health care provider about all the medicines you take including prescription and non-prescription medicines, vitamins, and herbal supplements. Sometimes, the doses of certain medicines and fentanyl transdermal system need to be changed when used together.

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

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

How do I use fentanyl transdermal system?

- Follow your health care provider's directions exactly. Your health care provider may change your dose based on your reactions to the medicine. Do not change your dose or stop using fentanyl transdermal system unless your health care provider tells you to. Do not use fentanyl transdermal system more often than prescribed. (See the end of this leaflet for "How and when to apply fentanyl transdermal system.")
- Do not wear more than <u>one</u> fentanyl transdermal system patch at a time, unless your health care provider tells you to do so.
- Call your health care provider right away if you get a fever higher than 102°F. A fever may cause too much of the medicine in fentanyl transdermal system to pass into your body. Your health care provider may tell you to use a lower dose while you have a fever.
- If you use too much fentanyl transdermal system or overdose, get emergency medical help right away.
- If you have concerns about addiction when using your pain medicine or if you have experienced drug or alcohol addiction in the past, talk to your health care provider.
- After you have stopped using a patch, be sure to fold the sticky sides of the patch together and flush it down the toilet. Do not put used fentanyl transdermal system patches in a garbage can.
- If your health care provider tells you to stop using fentanyl transdermal system, throw away the unused packages. Open the unused packages and fold the sticky sides of the patches together, and flush them down the toilet.

What should I avoid while using fentanyl transdermal system?

- **Do not use heat sources such as heating pads, electric blankets, heat lamps, saunas, hot tubs, or heated waterbeds. Do not take long hot baths or sun bathe.** All of these can make your temperature rise and cause too much of the medicine in fentanyl transdermal system to pass into your body.
- **Do not breast feed unless your health care provider tells you it is okay.** Fentanyl transdermal system passes into your milk and can cause serious problems for your baby.
- **Do not take other medicines without talking to your health care provider.** Other medicines include prescription and non-prescription medicines, vitamins, and herbal supplements. **Be especially careful about other medicines that make you sleepy.**
- **DO NOT DRINK ANY ALCOHOL WHILE USING FENTANYL TRANSDERMAL SYSTEM.** IT CAN INCREASE YOUR CHANCES OF HAVING DANGEROUS SIDE EFFECTS.
- **DO NOT DRIVE, OPERATE HEAVY MACHINERY, OR DO OTHER POSSIBLY DANGEROUS ACTIVITIES** UNITL YOU KNOW HOW FENTANYL TRANSDERMAL SYSTEM AFFECTS YOU. FENTANYL TRANSDERMAL SYSTEM CAN MAKE YOU SLEEPY. ASK YOUR HEALTH CARE PROVIDER TO TELL YOU WHEN IT IS OKAY TO DO THESE ACTIVITIES.
- **DO NOT STOP USING FENTANYL TRANSDERMAL SYSTEM SUDDENLY.** YOUR BODY CAN DEVELOP A PHYSICAL DEPENDENCE ON FENTANYL TRANSDERMAL SYSTEM. YOU CAN GET SICK IF YOU SUDDENLY STOP USING IT. TALK TO YOUR HEALTH CARE PROVIDER ABOUT HOW TO SAFELY STOP USING FENTANYL TRANSDERMAL SYSTEM.

What are the possible side effects of fentanyl transdermal system?

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

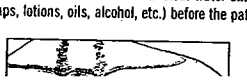
Call your health care provider right away or get emergency medical help if you have trouble breathing or have other serious side effects while using fentanyl transdermal system.

- The most common side effects with fentanyl transdermal system are nausea, vomiting, constipation, dry mouth, sleepiness, confusion, weakness, and sweating. Although uncommon, trouble sleeping and seizures were reported in children. These are not all the possible side effects of fentanyl transdermal system. For a complete list, ask your health care provider or pharmacist.
- Talk to your health care provider about any side effect that concerns you.

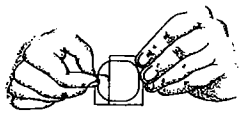
How and where to apply fentanyl transdermal system

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

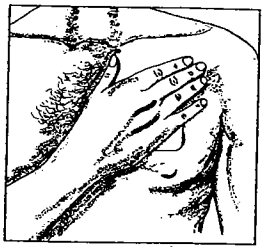
1. **Prepare:** For adults, put the patch on the chest, back, flank (sides of the waist), or upper arm in a place where there is no hair. Put it on right away after you have removed it from the pouch. Avoid sensitive areas or those that move around a lot. If there is hair, **do not shave (shaving irritates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



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



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



- Each fentanyl transdermal system patch is sealed in its own protective pouch. Do not remove the fentanyl transdermal system patch from the pouch until you are ready to use it. When you are ready to put on fentanyl transdermal system, tear open the pouch and remove the fentanyl transdermal system patch.
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- Wash your hands when you have finished applying fentanyl transdermal system.
- Remove fentanyl transdermal system after wearing it for 3 days (see "Disposing of fentanyl transdermal system"). Choose a *different* place on the skin to apply a new fentanyl transdermal system patch and repeat Steps 1 through 3. **Do not apply the new patch to the same place as the last one.**

When to apply fentanyl transdermal system

- You can apply fentanyl transdermal system at any time of the day. Change it at about the same time of day 3 days later or as directed by your health care provider.
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Water and fentanyl transdermal system

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

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Inactive ingredients: Dimethicone NF, silicone adhesive and polyolefin film backing.

MYLAN®

Mylan Pharmaceuticals Inc.
Morgantown, WV 26505

REVISED NOVEMBER 2003
PL:FTS:R2

Patient Information
FENTANYL TRANSDERMAL SYSTEM

CII

℞ only

This leaflet contains important information about fentanyl transdermal system. Read this patient information carefully before you start using fentanyl transdermal system. Read it each time you get a prescription. There may be new information. This information does not take the place of talking to your health care provider about your medical condition or your treatment. Only your health care provider can decide if fentanyl transdermal system is the right treatment for you. If you do not understand some of this information or have questions, talk with your health care provider.

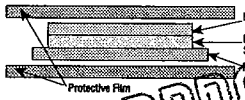
What is the most important information I should know about fentanyl transdermal system?

- **Only use fentanyl transdermal system the way your health care provider recommends.**
- **Fentanyl transdermal system contains fentanyl, a narcotic pain medicine that if taken the wrong way can lead to serious problems, including overdose and death.**
- **Fentanyl transdermal system should only be used to treat chronic (continuing) pain that is moderate to severe.**
  - When strong pain medicines are needed, and
  - When pain medicine is needed around the clock (all the time)
- **Fentanyl transdermal system should not be used to treat pain that will last only a few days.** This includes the pain that happens with surgery, medical, or dental procedures.
- **Fentanyl transdermal system should only be used in children age 2 years or older who are already using other narcotic pain medicines (opioid tolerant).** Fentanyl transdermal system has not been studied in children who are less than 2 years of age. It is not known if fentanyl transdermal system would be safe in these children.
- **Only use fentanyl transdermal system for the condition for which it was prescribed.**

What is fentanyl transdermal system?

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

(Diagram Not to Scale)



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Do not use fentanyl transdermal system:

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

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

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

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

- Fentanyl transdermal system can be used in children 2 years or older only if they are opioid-tolerant. These are children who are using other narcotic pain medicines for continuing pain right before starting fentanyl transdermal system.
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- Keep this medicine in a safe place. Keep fentanyl transdermal system out of the reach of children.

How do I use fentanyl transdermal system?

- Follow your health care provider's directions exactly. Your health care provider may change your dose based on your reactions to the medicine. Do not change your dose or stop using fentanyl transdermal system unless your health care provider tells you to. Do not use fentanyl transdermal system more often than prescribed. (See the end of this leaflet for "How and when to apply fentanyl transdermal system.")
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- Call your health care provider right away if you get a fever higher than 102°F. A fever may cause too much of the medicine in fentanyl transdermal system to pass into your body. Your health care provider may tell you to use a lower dose while you have a fever.
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- If you have concerns about addiction when using your pain medicine or if you have experienced drug or alcohol addiction in the past, talk to your health care provider.
- After you have stopped using a patch, be sure to fold the sticky sides of the patch together and flush it down the toilet. Do not put used fentanyl transdermal system patches in a garbage can.
- If your health care provider tells you to stop using fentanyl transdermal system, throw away the unused packages. Open the unused packages and fold the sticky sides of the patches together, and flush them down the toilet.

What should I avoid while using fentanyl transdermal system?

- **Do not use heat sources such as heating pads, electric blankets, heat lamps, saunas, hot tubs, or heated waterbeds. Do not take long hot baths or sun bathe.** All of these can make your temperature rise and cause too much of the medicine in fentanyl transdermal system to pass into your body.
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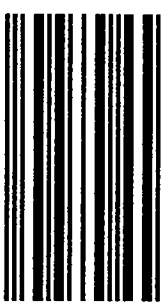
- **DO NOT DRIVE, OPERATE HEAVY MACHINERY, OR DO OTHER POSSIBLY DANGEROUS ACTIVITIES** UNTIL YOU KNOW HOW FENTANYL TRANSDERMAL SYSTEM AFFECTS YOU. FENTANYL TRANSDERMAL SYSTEM CAN MAKE YOU SLEEPY. ASK YOUR HEALTH CARE PROVIDER TO TELL YOU WHEN IT IS OKAY TO DO THESE ACTIVITIES.
- **DO NOT STOP USING FENTANYL TRANSDERMAL SYSTEM SUDDENLY.** YOUR BODY CAN DEVELOP A PHYSICAL DEPENDENCE ON FENTANYL TRANSDERMAL SYSTEM. YOU CAN GET SICK IF YOU SUDDENLY STOP USING IT. TALK TO YOUR HEALTH CARE PROVIDER ABOUT HOW TO SAFELY STOP USING FENTANYL TRANSDERMAL SYSTEM.

What are the possible side effects of fentanyl transdermal system?

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

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

- The most common side effects with fentanyl transdermal system are nausea, vomiting, constipation, dry mouth, sleepiness, confusion, weakness, and sweating. Although uncommon, trouble sleeping and seizures were reported in children. These are not all the possible side effects of fentanyl transdermal system. For a complete list, ask your health care provider or pharmacist.
- Talk to your health care provider about any side effect that concerns you.



"SPECIMEN"

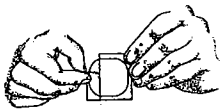
58
16-28

How and where to apply fentanyl transdermal system

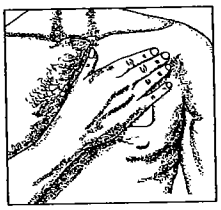
IN THE HOSPITAL, YOUR HEALTH CARE PROVIDER OR OTHER MEDICAL PERSON WILL APPLY FENTANYL TRANSDERMAL SYSTEM FOR YOU. AT HOME, YOU OR A MEMBER OF YOUR FAMILY MAY APPLY FENTANYL TRANSDERMAL SYSTEM TO YOUR SKIN. YOU NEED TO CHECK THE PATCHES OFTEN TO MAKE SURE THAT THEY ARE STICKING WELL TO THE SKIN. IN YOUNG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

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

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



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



- Each fentanyl transdermal system patch is sealed in its own protective pouch. Do not remove the fentanyl transdermal system patch from the pouch until you are ready to use it. When you are ready to put on fentanyl transdermal system, tear open the pouch and remove the fentanyl transdermal system patch.
- Do not put the fentanyl transdermal system patch on skin that is very oily, burned, broken out, cut, irritated, or damaged in any way.
- If you have any questions about where on your body you should or should not apply the patch, please ask your health care provider.
- Fentanyl transdermal system may not stick to all patients. If the patch does not stick well or comes loose after applying, tape the edges down with first aid tape. If the patch falls off, throw it away and put a new one on at a different skin site (see "Disposing of fentanyl transdermal system").
- Wash your hands when you have finished applying fentanyl transdermal system.
- Remove fentanyl transdermal system after wearing it for 3 days (see "Disposing of fentanyl transdermal system"). Choose a *different* place on the skin to apply a new fentanyl transdermal system patch and repeat Steps 1 through 3. **Do not apply the new patch to the same place as the last one.**

When to apply fentanyl transdermal system

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

Water and fentanyl transdermal system

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

Disposing of fentanyl transdermal system

- BEFORE PUTTING ON A NEW FENTANYL TRANSDERMAL SYSTEM PATCH, REMOVE THE PATCH YOU HAVE BEEN WEARING.
- FOLD THE USED FENTANYL TRANSDERMAL SYSTEM PATCH IN HALF SO THAT THE STICKY SIDE STICKS TO ITSELF. **FLUSH THE USED FENTANYL TRANSDERMAL SYSTEM DOWN THE TOILET RIGHT AWAY. A USED FENTANYL TRANSDERMAL SYSTEM PATCH MAY BE DANGEROUS FOR OR EVEN LEAD TO DEATH IN BABIES, CHILDREN, PETS, AND ADULTS WHO HAVE NOT BEEN PRESCRIBED FENTANYL TRANSDERMAL SYSTEM.**
- THROW AWAY ANY FENTANYL TRANSDERMAL SYSTEM PATCHES THAT ARE LEFT OVER FROM YOUR PRESCRIPTION AS SOON AS THEY ARE NO LONGER NEEDED. REMOVE THE LEFTOVER PATCHES FROM THEIR PROTECTIVE POUCH AND REMOVE THE PROTECTIVE LINER. **FOLD THE PATCHES IN HALF WITH THE STICKY SIDES TOGETHER, AND FLUSH THE PATCHES DOWN THE TOILET.** DO NOT FLUSH THE POUCH OR THE PROTECTIVE LINER DOWN THE TOILET. THESE ITEMS CAN BE THROWN AWAY IN A GARBAGE CAN.

Safety and handling of fentanyl transdermal system

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

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

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

How should fentanyl transdermal system be stored?

STORE FENTANYL TRANSDERMAL SYSTEM BELOW 77°F (25°C). REMEMBER, THE INSIDE OF YOUR CAR CAN REACH TEMPERATURES MUCH HIGHER THAN THIS IN THE SUMMER. DO NOT REFRIGERATE.

KEEP FENTANYL TRANSDERMAL SYSTEM IN ITS PROTECTIVE POUCH UNTIL YOU ARE READY TO USE IT.

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

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

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

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

FOR QUESTIONS ABOUT FENTANYL TRANSDERMAL SYSTEM CALL MYLAN PHARMACEUTICALS INC. PRODUCT INFORMATION AT 1-877 4 INFO-RX (1-877-446-3679) 8 A.M. TO 5 P.M. EST, MONDAY THROUGH FRIDAY.

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

WHAT ARE THE INGREDIENTS OF FENTANYL TRANSDERMAL SYSTEM?

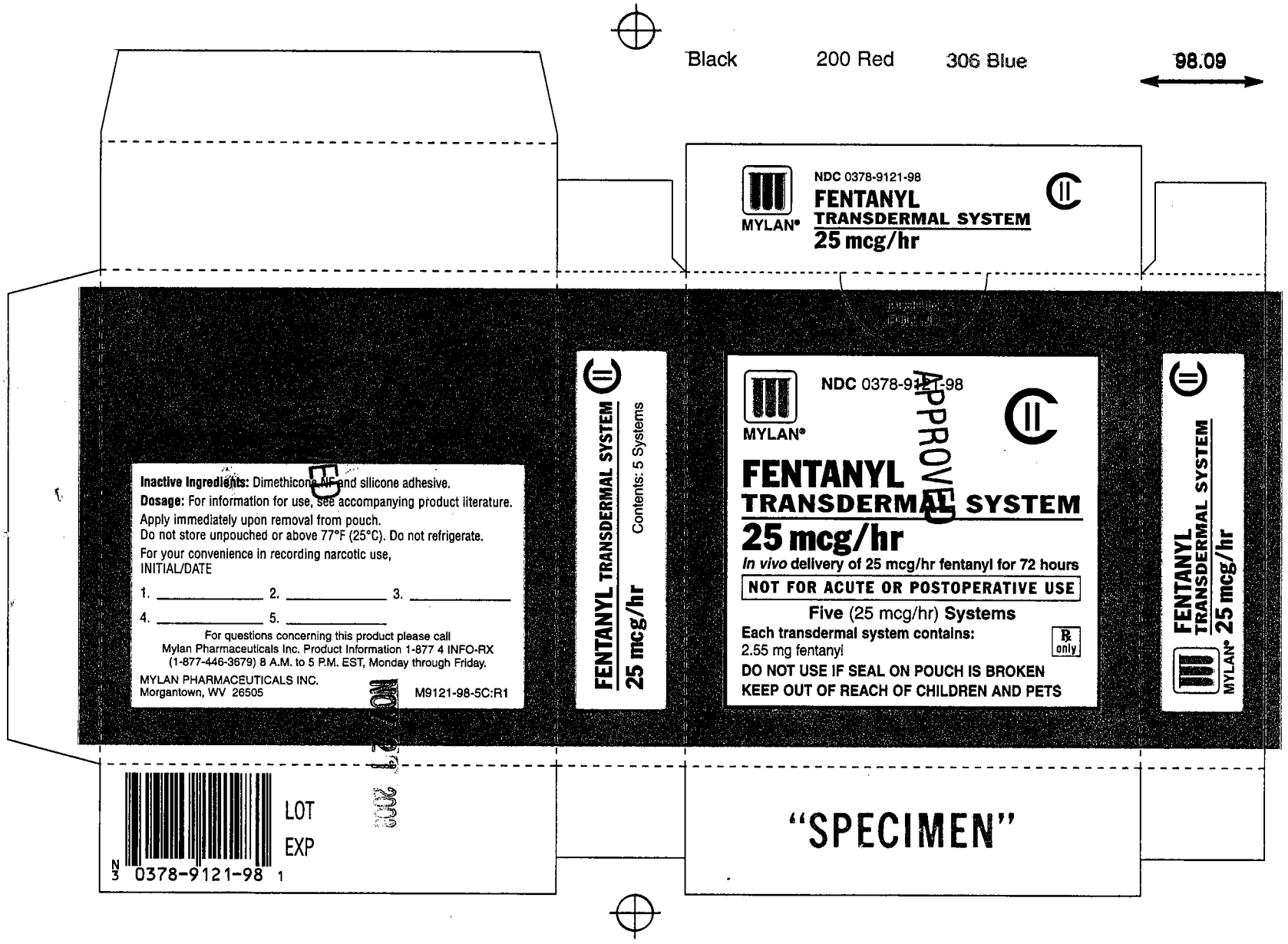
ACTIVE INGREDIENT: FENTANYL

Inactive ingredients: Dimethicone NF, silicone adhesive and polyolefin film backing.

MYLAN®

Mylan Pharmaceuticals Inc.
Morgantown, WV 26505

REVISED NOVEMBER 2003
PL:FTS:R2


Black 200 Red 306 Blue 98.09
MYLAN®
NDC 0378-9121-98
FENTANYL
TRANSDERMAL SYSTEM
25 mcg/hr
Inactive Ingredients: Dimethicone NF and silicone adhesive.
Dosage: For information for use, see accompanying product literature.
Apply immediately upon removal from pouch.
Do not store unpouched or above 77°F (25°C). Do not refrigerate.
For your convenience in recording narcotic use,
INITIAL/DATE
1. _____ 2. _____ 3. _____
4. _____ 5. _____
For questions concerning this product please call
Mylan Pharmaceuticals Inc. Product Information 1-877 4 INFO-RX
(1-877-446-3679) 8 A.M. to 5 P.M. EST, Monday through Friday.
MYLAN PHARMACEUTICALS INC.
Morgantown, WV 26505
M9121-98-5C:R1
FENTANYL TRANSDERMAL SYSTEM
25 mcg/hr
Contents: 5 Systems
NDC 0378-9121-98
APPROVED
FENTANYL
TRANSDERMAL SYSTEM
25 mcg/hr
In vivo delivery of 25 mcg/hr fentanyl for 72 hours
NOT FOR ACUTE OR POSTOPERATIVE USE
Five (25 mcg/hr) Systems
Each transdermal system contains:
2.55 mg fentanyl
℞ only
DO NOT USE IF SEAL ON POUCH IS BROKEN
KEEP OUT OF REACH OF CHILDREN AND PETS
FENTANYL
TRANSDERMAL SYSTEM
25 mcg/hr
MYLAN®
LOT
EXP
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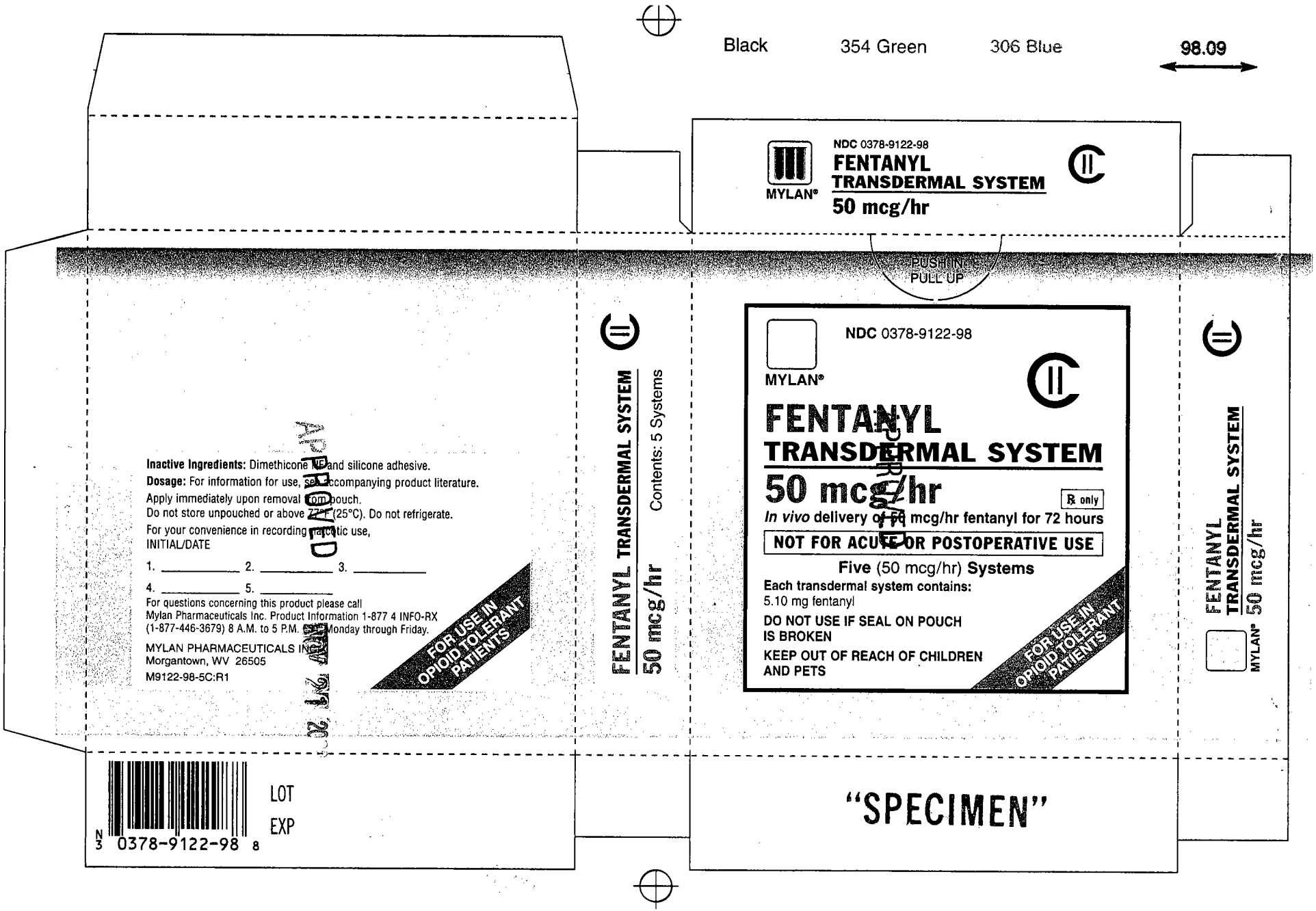
Black
354 Green
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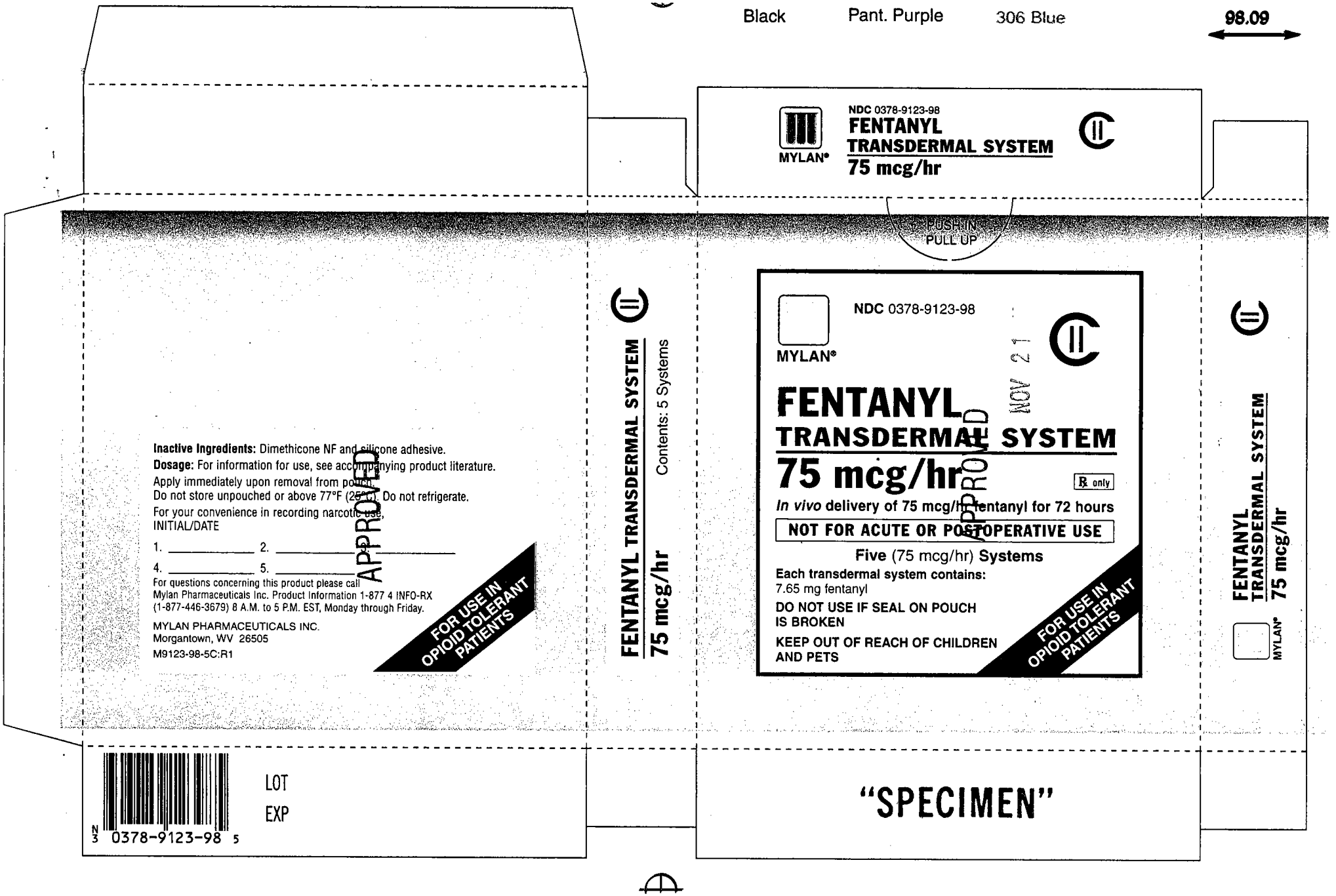
NDC 0378-9122-98
FENTANYL
TRANSDERMAL SYSTEM
50 mcg/hr
MYLAN®
PUSH IN
PULL UP
NDC 0378-9122-98
MYLAN®
FENTANYL
TRANSDERMAL SYSTEM
50 mcg/hr
Rx only
In vivo delivery of 50 mcg/hr fentanyl for 72 hours
NOT FOR ACUTE OR POSTOPERATIVE USE
Five (50 mcg/hr) Systems
Each transdermal system contains:
5.10 mg fentanyl
DO NOT USE IF SEAL ON POUCH IS BROKEN
KEEP OUT OF REACH OF CHILDREN AND PETS
FOR USE IN OPIOID TOLERANT PATIENTS
FENTANYL TRANSDERMAL SYSTEM
50 mcg/hr
Contents: 5 Systems
Inactive Ingredients: Dimethicone fluid and silicone adhesive.
Dosage: For information for use, see accompanying product literature.
Apply immediately upon removal from pouch.
Do not store unpouched or above 77°F (25°C). Do not refrigerate.
For your convenience in recording therapeutic use,
INITIAL/DATE
1. _____ 2. _____ 3. _____
4. _____ 5. _____
For questions concerning this product please call
Mylan Pharmaceuticals Inc. Product Information 1-877 4 INFO-RX
(1-877-446-3679) 8 A.M. to 5 P.M. EST Monday through Friday.
MYLAN PHARMACEUTICALS INC.
Morgantown, WV 26505
M9122-98-5C:R1
FOR USE IN OPIOID TOLERANT PATIENTS
N 3 0378-9122-98 8
LOT
EXP
"SPECIMEN"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Pant. Purple
306 Blue
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MYLAN®
NDC 0378-9123-98
FENTANYL
TRANSDERMAL SYSTEM
75 mcg/hr
PUSH IN
PULL UP
NDC 0378-9123-98
MYLAN®
FENTANYL
TRANSDERMAL SYSTEM
75 mcg/hr
Rx only
In vivo delivery of 75 mcg/hr fentanyl for 72 hours
NOT FOR ACUTE OR POSTOPERATIVE USE
Five (75 mcg/hr) Systems
Each transdermal system contains:
7.65 mg fentanyl
DO NOT USE IF SEAL ON POUCH IS BROKEN
KEEP OUT OF REACH OF CHILDREN AND PETS
FOR USE IN OPIOID TOLERANT PATIENTS
APPROVED
NOV 21 12 AM
Inactive Ingredients: Dimethicone NF and silicone adhesive.
Dosage: For information for use, see accompanying product literature.
Apply immediately upon removal from pouch.
Do not store unpouched or above 77°F (25°C). Do not refrigerate.
For your convenience in recording narcotic use,
INITIAL/DATE
1. _____ 2. _____
4. _____ 5. _____
For questions concerning this product please call
Mylan Pharmaceuticals Inc. Product Information 1-877 4 INFO-RX
(1-877-446-3679) 8 A.M. to 5 P.M. EST, Monday through Friday.
MYLAN PHARMACEUTICALS INC.
Morgantown, WV 26505
M9123-98-5C:R1
FOR USE IN OPIOID TOLERANT PATIENTS
FENTANYL TRANSDERMAL SYSTEM
75 mcg/hr
Contents: 5 Systems
FENTANYL
TRANSDERMAL SYSTEM
75 mcg/hr
MYLAN®
N 3 0378-9123-98 5
LOT
EXP
"SPECIMEN"

Black 124 Yellow 306 Blue 98.09

MYLAN®

NDC 0378-9124-98

FENTANYL TRANSDERMAL SYSTEM

100 mcg/hr

PUSH IN
PULL UP

Inactive Ingredients: Dimethicone NF and silicone adhesive.

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

Apply immediately upon removal from pouch.

Do not store unpouched or above 77°F (25°C). Do not refrigerate.

For your convenience in recording narcotic use,
INITIAL/DATE

1. _____ 2. _____ 3. _____

4. _____ 5. _____

For questions concerning this product please call
Mylan Pharmaceuticals Inc. Product Information 1-877 4 INFO-RX
(1-877-446-3679) 8 A.M. to 5 P.M. EST, Monday through Friday.

MYLAN PHARMACEUTICALS INC.
Morgantown, WV 26505

M9124-98-5C:R1

APPROVED

TRANSDERMAL SYSTEM

Contents: 5 Systems

NDC 0378-9124-98

MYLAN®

FENTANYL

TRANSDERMAL SYSTEM

100 mcg/hr

℞ only

In vivo delivery of 100 mcg/hr fentanyl for 72 hours

NOT FOR ACUTE OR POSTOPERATIVE USE

Five (100 mcg/hr) **Systems**

Each transdermal system contains:
10.20 mg fentanyl

DO NOT USE IF SEAL ON POUCH IS BROKEN

KEEP OUT OF REACH OF CHILDREN AND PETS

APPROVED NOV 21

TRANSDERMAL SYSTEM

MYLAN®

N 3 0378-9124-98 2

LOT

EXP

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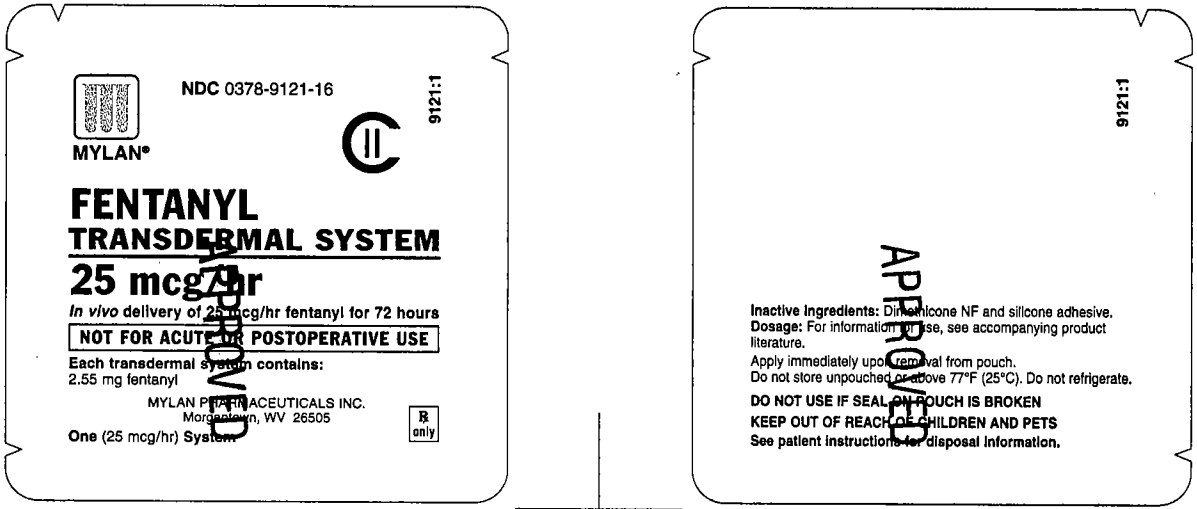
"SPECIMEN"



NOV 21 2003

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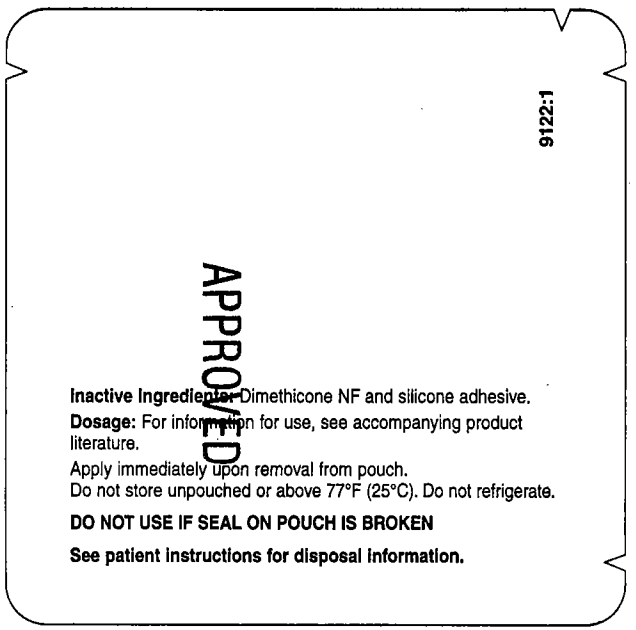

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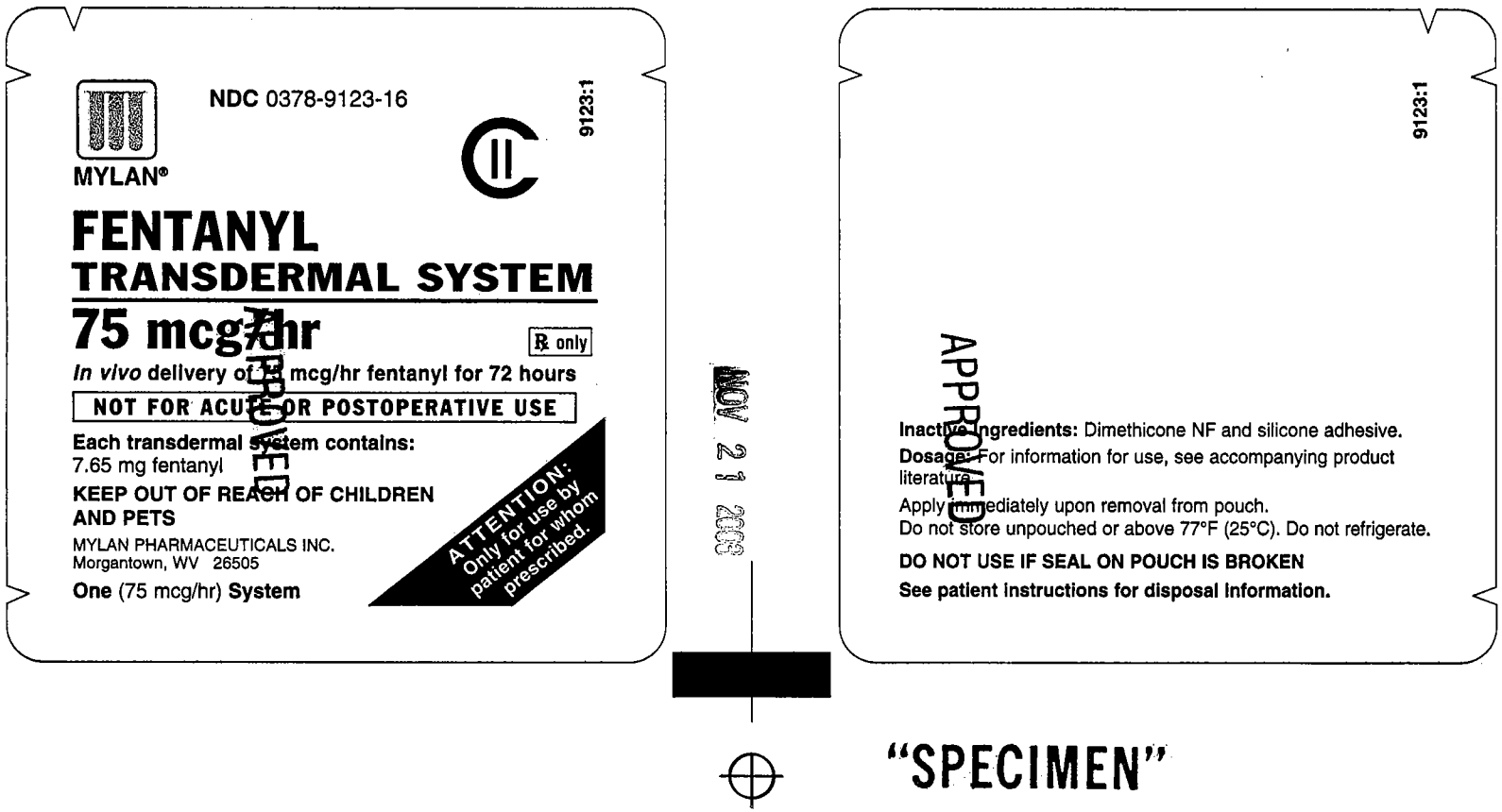

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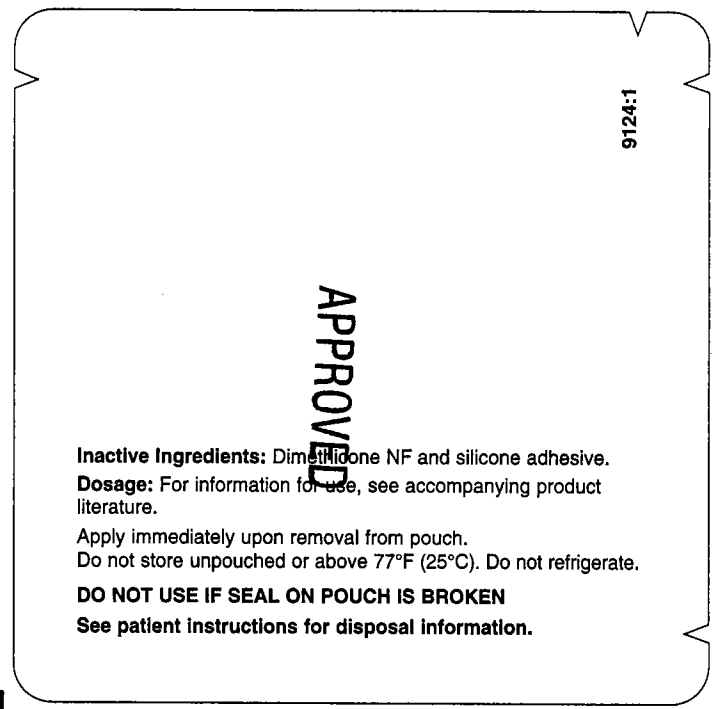

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

76-258

CSO LABELING REVIEW(S)

(APPROVAL SUMMARY)
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

Superseded by approval summary for NDA 20,200 Supplement

ANDA Number: 76-258 Date of Submission: June 20, 2002 and August 7, 2002

Applicant's Name: Mylan Technologies, Inc.

Established Name: Fentanyl Transdermal System, 25 mcg/hr, 50 mcg/hr, 75 mcg/hr & 100 mcg/hr

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):

Do you have 12 Final Printed Labels and Labeling? Yes

CONTAINER LABELS (Pouch Labels) - 25 mcg/hr, 50 mcg/hr, 75 mcg/hr & 100 mcg/hr

Satisfactory in FPL as of 6/20/02 submission (Code# - 9212:1, Section B)

PATCH LABELS (Backside of the Patch)

Satisfactory in FPL as of 6/20/02 submission
*Actually submitted in draft, but we will accept as FPL as we do for the blister labels for the solid oral dosage forms.

CARTON LABELING - Five systems of 25 mcg/hr, 50 mcg/hr, 75 mcg/hr & 100 mcg/hr

Satisfactory in FPL as of 6/20/02 submission (M9121-98-5C:R1, Section B)

PROFESSIONAL PACKAGE INSERT LABELING:

Satisfactory in FPL as of **8/7/02** submission (FTS:R2, Rev. 7/02)

PATIENT INSTRUCTIONS LABELING:

Satisfactory in FPL as of 6/20/02 submission (PL:FTS:R1, Rev. 4/02)

REVISIONS NEEDED POST-APPROVAL:

None

BASIS OF APPROVAL:

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: Duragesic® patch

NDA Number: NDA 19-813/S-030

NDA Drug Name: Duragesic® patch

NDA Firm: ALZA Corp.

Date of Approval of NDA Insert and supplement #:

APPEARS THIS WAY
ON ORIGINAL

19-813/S-030, approved April 9, 2001

Has this been verified by the MIS system for the NDA?
Yes

Was this approval based upon an OGD labeling guidance? No

Basis of Approval for the Container labels and Carton labeling: Side-by-side comparison with the innovator's labeling

Other Comments:

See FTR for BE issue.

QUESTIONS/NOTE TO THE CHEMIST (Sent to the chemist and Bio. reviewer via e-mail on 3/29/02)

We note that the sponsor's proposed transdermal system is quite different form the one of the innovator. The followings are my question regarding the sponsor' s proposal.

1. **The sponsor's proposal does not have a drug reservoir for fentanyl as opposed to the innovator. Is it acceptable?**

2. **The sponsor's proposal does not contain a membrane that controls the rate of fentanyl delivery to the skin surface while the innovator's product has an ethylene-vinyl acetate copolymer membrane for this action. How does the sponsor's transdermal system control the drug delivery? Both the innovator and sponsor's systems has "Fentanyl containing silicone adhesive" layer.**

3. **Under "Pharmacokinetics" subsection we find the following text. Are these accurate statements?**

   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 release. Fentanyl moves in the direction of the lower concentration at a rate determined by the diffusion of fentanyl through skin layers.

4. **One more question:**

   The innovator claims that the [redacted] Is it acceptable?

Answer from Chemist on 4/2/02

Glen made the following comments regarding your questions:

1. Yes, it is acceptable that the proposed drug product does not have a drug reservoir.
2. If there is an excess amount of drug on the adhesive, then the rate of diffusion will follow first order kinetics, i.e. the rate will be constant.
3. Yes, the statement is correct.
4. Yes, the innovator's drug product has [redacted]. However, we do not know if the presence of [redacted] Fentanyl to the skin.

Tao-Chin

FOR THE RECORD:

1. MODEL LABELING - Duragesic package insert labeling. (NDA 19-813/S-030, approved 4/9/01). The most current PPI (rev. April, 1998) was obtained form the PM in the new drug division (See file folder).

2. This drug product is **not** the subject of a USP monograph.

3. This application appears the **FIRST** generic.

4. The sponsor submitted an amendment dated December 4, 2001 for the additional strengths of 50 mcg/hr, 75 mcg/hr & 100 mcg/hr.

5. The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition appearing on page 2325 (Volume B.1.2).

6. PATENTS/EXCLUSIVITIES

Patent Data

Appl No	Prod No	Patent No	Patent Expiration	Use Code
019813	001	4588580	JUL 23,2004	U-43

U- 43: MANAGEMENT OF CHRONIC PAIN IN PATIENTS REQUIRING OPIOID ANALGESIA

Exclusivity Data

There is no unexpired exclusivity for this product.

The firm's statement is accurate. **They filed a paragraph IV.**

7. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON7

RLD - Do not store above 77oF (25oC).

ANDA - Do not store above 25oC (77oF). Do not refrigerate. The sponsor did not stability studies in the refrigeration temperature and that's the reason to retain the statement "do not refrigerate.". We find this acceptable.

8. PACKAGING CONFIGURATIONS

RLD & ANDA - 5s of 25 mcg/hr, 50 mcg/hr, 75 mcg/hr & 100 mcg/hr.

9. These drug products are solely manufactured by Mlylan, Inc.

10. The sponsor proposed one PPI per one carton of 5 systems. The innovator also contain one PPI per carton of 5 systems as I found out by contacting the CMH Pharmacy on July 18, 2002. We find this acceptable.

11. The sponsor's proposal for the transdermal system is significantly different from that of the innovator. Refer to the questions/answers to/from the chemist above.

12. I spoke with the bio. reviewer, Dr. Tran on the phone on 7/19/02 addressing the different transdermal system and formulation proposed by the sponsor. He stated that the bio review of this system is comparable to that of the controlled-release solid oral dosage form. As long as the

result from the ***in vivo*** bio study is equivalent to that of innovator, then it should be acceptable for an approval with the labeling modeled after the RLD labeling in terms of CLINICAL PHARMACOLOGY section. However, he stated that in addition to the bio. data, the clinical aspects of this product such as skin irritability should be also addressed. I believe the bio reviewer send a consult to the new drug division to address this clinical aspects.

Date of Review: August 22, 02 **Date of Submission: June 20 & August 7, 02**

Primary Reviewer: Chan Park **Date:** 8/26/02

Acting Team Leader: Lillie Golson **Date:** 8/26/02

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cc:

ANDA: 76-258
DUP/DIVISION FILE
HFD-613/CPark/ LGolson (no cc)
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Review

APPEARS THIS WAY
ON ORIGINAL

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 76-258 Date of Submission: October 12, 2001 & December 4, 2001

Applicant's Name: Mylan Technologies, Inc.

Established Name: Fentanyl Transdermal System, 25 mcg/hr, 50 mcg/hr, 75 mcg/hr & 100 mcg/hr

Labeling Deficiencies:

1. GENERAL COMMENT

   a. Please increase the prominence of the controlled substance symbol. We refer you to 21 CFR 1302.04.

   b. It is preferable to use the term "mcg" rather than '

2. POUCH

   a. See the general comments above.

   b. We note that you listed "polyolefin film" as one of the inactive ingredients contained in your drug products. However, according to the components and composition statements, it was used for the backing film for the transdermal system. Please delete and/or clarify

   d. We note that your storage temperature statement is different from the innovator's statement. Please revise to be the same or validate your proposal by submitted supporting data.

3. CARTON

   a. See the comments under CONTAINER above.

   b. Considering that some patients may not be familiar with your unique transdermal system, we ask that you may consider including a similar guiding statement regarding questions on your drug products as does the innovator.

4. INSERT

   a. GENERAL

      i. See the general comments above.

      ii. Replace the proprietary name with "Fentanyl transdermal system" rather than ' ' throughout the text .

      iii. Please note that USAN names are common nouns and should be treated as such in the text of labeling (*i.e.*, lower case). Upper case may be used when the USAN name stands alone as on labels or in the title of the package insert.

      iv. It is preferable to use the term "to" rather than a ' ' when expressing a numerical range.

   b. BOXED WARNING - First bullet:

      ... acting opioids and [pleural]

c. DESCRIPTION

i. First paragraph:

...piperidyl] proponamide. [spelling]

ii. Diagram

Please revise to read "Fentanyl containing Silicon Adhesive" rather than [redacted] and/or comment.

iii. Last paragraph - Add the following text to read:

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

d. CLINICAL PHARMACOLOGY, Ventilatory Effects - First paragraph, Penultimate sentence:

...naïve post-operative patients... [add "post-"]

e. PRECAUTIONS - Patients with Fever/External Heat, Second paragraph:

...system application site to direct... [add "site"]

f. HOW SUPPLIED

i. Please assure that you print the entire text of Patient Information Leaflet at the end of insert labeling in addition to the separate Patient Information Leaflet to be dispensed to the patients. See 21 CFR 201.57(f)(2) for guidance.

ii. Safety and Handling

See the comment 4c(iii) above.

iii. See the comment 2(d) above.

5. PATIENT INFORMATION LEAFLET

a. GENERAL

Describe your plans for supplying the patient information leaflet with your product, e.g., how many leaflets will you supply for each carton and how will these leaflets be supplied.

b. What is Fentanyl Transdermal System

See the comment 4c(ii) above.

c. How and Where to Apply Fentanyl Transdermal System (Step 2)

i. First sentence:

[redacted]

ii. Third sentence - Revise to read as follows to be in accordance with the schematic drawing of your proposed system:

[redacted]

iii. [redacted]

d. When to apply Fentanyl Transdermal System - Second paragraph:

...TO HAVE PAIN, CALL... [add a comma]

e. Safety and Handling

See the comment 4c(iii) above.

f. Storage Instructions

i. See the comment 2(d) above.

ii. See the comment 3(b) above.

Please revise your labels and labeling, as instructed above, and submit 4 draft copies for a tentative approval or 12 final printed copies for a full approval of this application. If draft labeling is provided, please be advised that you will be required to submit 12 final printed copies of all labels and labeling at least 60 days prior to full approval of this application. In addition, you should be aware that color and other features (print size, prominence, etc) in final printed labeling could be found unacceptable and that further changes might be requested prior to approval.

Prior to approval, it may be necessary to further revise your labeling subsequent to approved changes for the reference listed drug. We suggest that you routinely monitor the following website for any approved changes-
http://www.fda.gov/cder/ogd/rld/labeling review branch.html

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

/s/ for

William Peter Rickman
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

QUESTIONS/NOTE TO THE CHEMIST (Sent to the chemist and Bio. reviewer via e-mail on 3/29/02)

We note that the sponsor's proposed transdermal system is quite different form the one of the innovator. The followings are my question regarding the sponsor' s proposal.

1. **The sponsor's proposal does not have a drug reservoir for fentanyl as opposed to the innovator. Is it acceptable?**

2. **The sponsor's proposal does not contain a membrane that controls the rate of fentanyl delivery to the skin surface while the innovator's product has an ethylene-vinyl acetate copolymer membrane for this action. How does the sponsor's transdermal system control the drug delivery? Both the innovator and sponsor's systems has "Fentanyl containing silicone adhesive" layer.**

3. **Under "Pharmacokinetics" subsection we find the following text. Are these accurate statements?**

   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 release. Fentanyl moves in the direction of the lower concentration at a rate determined by the diffusion of fentanyl through skin layers.

4. **One more question:**

   [redacted] **Is it acceptable?**

Answer from Chemist on 4/2/02

Glen made the following comments regarding your questions:

1. Yes, it is acceptable that the proposed drug product does not have a drug reservoir.
2. If there is an excess amount of drug on the adhesive, then the rate of diffusion will follow first order kinetics, i.e. the rate will be constant.
3. Yes, the statement is correct.
4. Yes, the innovator's drug product has [redacted]. However, we do not know if the presence of [redacted] Fentanyl to the skin.

Tao-Chin

FOR THE RECORD:

1. MODEL LABELING - Duragesic package insert labeling. (NDA 19-813/S-013 & S-030, approved 4/9/01). The most current PPI (rev. April, 1998) was obtained form the PM in the new drug division (See file folder).

2. This drug product is **not** the subject of a USP monograph.

3. This application appears the **FIRST** generic.

4. The sponsor submitted an amendment dated December 4, 2001 for the additional strengths of 50 mcg/hr, 75 mcg/hr & 100 mcg/hr.

5. The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and

composition appearing on page 2325 (Volume B.1.2). However, see the comment 2(c) above.

6. PATENTS/EXCLUSIVITIES

Patent Data

Appl No	Prod No	Patent No	Patent Expiration	Use Code
019813	001	4588580	JUL 23,2004	U-43

U- 43: MANAGEMENT OF CHRONIC PAIN IN PATIENTS REQUIRING OPIOID ANALGESIA

Exclusivity Data

There is no unexpired exclusivity for this product.

The firm's statement is accurate. They filed a paragraph IV.

7. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON7

RLD - Do not store 77oF (25oC).

ANDA - Store at room temperature 15o - 30oC (59o - 86oF). Do not refrigerate. See comment above.

8. PACKAGING CONFIGURATIONS

RLD & ANDA - 5s of 25 mcg/hr, 50 mcg/hr, 75 mcg/hr & 100 mcg/hr.

9. These drug products are solely manufactured by Mlylan, Inc.

10. The sponsor's proposal for the transdermal system is significantly different from that of the innovator. Refer to the questions/answers to/from the chemist above.

11. There was no response from the bio. yet. It appears that the bio. review has not been done yet. The response from the chemist was forwarded to the bio. reviewer on 4/8/02. In Addison, acting team leader, Lillie Golson sent another e-mail to Bio. reviewer in this regard on 4/11/02.

Date of Review: April 8, 2002 Date of Submission: October 12, 2001 & December 4, 2001

Primary Reviewer: Chan Park C Park **Date:** 4/15/02

Acting Team Leader: LG Golson **Date:** 4/15/02

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cc:

ANDA: 76-258
DUP/DIVISION FILE
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Review

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

76-258

MEDICAL OFFICER REVIEW(S)

MEDICAL OFFICER REVIEW
January 24, 2001

ANDA 76-258
Drug Product: Fentanyl Transdermal System, 25 ug/h
Sponsor: Mylan Technologies, Inc.
Reference Listed Drug: Duragesic® (Janssen)

BACKGROUND

In the context of evaluating the bioequivalence of a transdermal generic drug product to its reference listed drug, skin irritation and sensitization studies are required. These should be done in humans and compare the skin irritation and sensitization potential of the generic and reference listed drug. The required testing is outlined in the *Guidance for Industry: Skin Irritation and Sensitization Testing of Generic Transdermal Drug Products* (12/99). Because of the abuse potential of fentanyl following repeated administration over the course of three weeks, it is recommended that a combined skin irritation and sensitization study comparing test and reference should be done using the lowest labeled dose. These studies should enroll patients for whom fentanyl is indicated or if normal volunteers are enrolled, subjects should be given naltraxone blockade.

PRODUCT DESCRIPTION

The reference listed drug is Duragesic®. It is a transdermal system that provides continuous delivery of fentanyl for 72 hours at an approximately continuous rate. The labeling for this drug product provides the following description of the system structure and components:

"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 delivery of fentanyl to the skin surface;
4) a fentanyl containing silicone adhesive. Before use, a protective liner covering the adhesive layer is removed and discarded."

Mylan's generic transdermal fentanyl is described in the ANDA submission in the following way:

> "System, Structure and Components – Fentanyl Transdermal System is a translucent rectangular patch with rounded corners comprising a protective liner and two functional layers. Proceeding from the outer surface towards the surface adhering to the skin, these layers are:

1) a backing layer of polyolefin film;
2) a fentanyl containing silicone adhesive layer.
3) 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. "

STUDIES SUBMITTED

The sponsor has submitted five studies that are listed below:

1. Repeated Exposure Sensitization Study Conducted with a Placebo formulation in Human Volunteers (FENT-0132)
2. A 21-Day, Randomized, Controlled Study to Evaluate the Local Tolerability of a Transdermal Delivery System for Fentanyl in Healthy Volunteers, using a Cumulative Irritant Patch Test Design (FENT-0133)
3. Evaluation of Contact Sensitization Potential of Fentanyl Transdermal System in Normal Healthy Volunteers (FENT-0134)
4. A Dermal Sensitization Study in Guinea Pigs
5. A Dermal Irritation Study in Rabbits

The recommended studies are to be conducted in humans and animal studies do not have a part in establishing the relative safety of the generic and the reference listed drug. The animal studies will not be reviewed.

I. TITLE: A Randomized, Controlled Study to Evaluate the Sensitizing Potential of a Transdermal Delivery System for Fentanyl in Healthy Volunteers, Using a Human Repeat Insult Patch Test Design (FENT-0132)

CRO: [redacted]

OBJECTIVE

The objective of this study was to determine the potential of the investigational Transdermal Delivery System for fentanyl to induce sensitization by repeated topical application to the healthy skin of humans under controlled conditions. In addition, safety was assessed by evaluation of any adverse events reported during the study.

STUDY DESIGN

This was a randomized, single-center, controlled, within-subject comparison study to evaluate the potential of contact sensitization of Mylan's fentanyl transdermal system as compared to a positive control (SLS) and a negative control (open unpatched). Three test articles were compared:

1. Fentanyl Transdermal System Placebo (FTS), Lot #R6J0007, test article
2. Sodium Lauryl Sulfate (SLS), 0.2% aqueous solution; positive control
3. Open unpatched area; negative control.

The study controls were evaluated under occlusive patch conditions by means of application of a [redacted] pad attached to a non-porous, plastic film adhesive bandage ([redacted]
The control patches were secured with hypoallergenic [redacted] tape as needed.

During the Induction period, the transdermal patches were applied 3 times a week for 48 hours except for Friday applications, which remained in place for 72 hours, for a total of 9 consecutive applications. Scoring for irritation was done prior to re-application of a new patch and after removal of the last patch. Any site reaching maximum irritation as defined below was not re-patched, but continued to be scored until the end of the study. In these cases, a patch was applied to an alternate site and scored as well for the remainder of the study.

A two-week Rest period in which the subjects did not receive any application of test article ensued and was followed by a Challenge.

One 48-hour application of each test system to a naïve site was used to test for reactions indicative of contact sensitization. The sites were evaluated at 48, and 96 hours post application. A re-challenge was carried out as appropriate and involved applying the test articles to a naïve site to confirm reactions indicative of contact sensitization.

Inclusion and exclusion criteria listed in the protocol were appropriate.

STUDY CONDUCT

Transdermal patches were applied to each subject's arm at the same site during the Induction phase of the study unless the maximum allowable irritation limit was reached (a score of ++, which was given the number grade 3). Patches remained in contact with the skin for 48 +/- 5 hours following a Monday or Wednesday application or 72 +/- 5 hours following a Friday application.

The primary measurement for the Induction phase was the evaluation of skin irritation approximately 30 minutes following patch removal. Following the Induction phase, subjects did not receive any application of the test systems during a Rest period of 10 to 17 days. The Challenge application was made on Monday of the sixth week on the arm opposite to that used for the Induction phase.

Local tolerability assessments used the following symbols to express the observed response:

Response:	Symbol
No reaction	-
Minimal or doubtful response, slightly different from surrounding normal	?

Definite erythema; no edema	+
Definite erythema; definite edema	++
Definite erythema; definite edema and vesiculation	+++

Response/Comment:

E = Marked/severe erythema
S = Spreading of reaction beyond patch study site (i.e., reaction where study material was not in contact with the skin)
B = Burning or stinging sensation
p = Papular response > 50%
pv = Papulovesicular response > 50%
D = Damage to epidermis; oozing, crusting and/or superficial erosions
I = Itching
X = Subject absent
PD = Patch dislodged
NA = Not applied
NP = Not patched (due to reaction achieved)
N9G = No ninth grading

Applications during the Induction phase were terminated or moved to an adjacent site if a strong reaction was observed. The maximum limits allowed were any reaction whose intensity was described as D, "++", or "+++".

Scoring convention:

Response Grade	Score
-	0
?	1
+	2
++, D or greater	3
p or pv	add 0.5 to erythema score

Adhesion scores were also measured but were not the subject of this review. Concomitant medications and adverse events were recorded at each visit.

STUDY RESULTS

Two hundred-thirty subjects were enrolled in the study. The study was conducted prior to 9/01. Thirty subjects discontinued the study. Three had protocol violations; 1 used ecotrin prior to entry and 2 did not return their patches. The remaining 27 subjects withdrew voluntarily for reasons unrelated to the study or were lost to follow-up. Two subjects completed the Induction phase but did not return for the challenge phase. Two hundred and two subjects were included in the analysis of cumulative skin irritation and two hundred were analyzed for sensitization.

Demographics

One hundred eighty-three (79.6%) subjects were Caucasian, twelve (5.2%) were African American, 25 (10.9%) were Hispanic, 3 (1.3%) were Asian, and 7 (3%) were of other races. One hundred seventy-two (74.8%) were female and 58 (25.2%) were male. Subjects ranged in age from 18 to 63 years old.

Mean Irritation Scores

Mean irritation, mean total irritation, total cumulative irritation, and the number of days until patch removal were calculated for each patch (Table I).

Table I
Mean Irritation Scores

Test Article	Mean Irritation	# of Subjects with (+) Erythema	# Discontinued due to Irritation	First Application (day) with Patch Removal
Fentanyl Placebo	0.53 +/- 0.55	50 (25%)	13 (6%)	5 (Day 12)
SLS	1.11 +/- 0.62	107 (53%)	26 (13%)	2 (Day 3)
Open	0.01 +/- 0.09	9.6	1	None

The Fentanyl placebo patch was significantly less irritating the SLS patch. The number of days until patch removal was not calculated for this study. However, SLS led to sufficient irritation to require patch removal much more frequently and much earlier in the study than did the generic placebo.

Skin Sensitization

Twenty subjects showed definite erythema (+) 30 minutes after patch removal that resolved after removal of the patches. This response was typical of cutaneous irritation and not a result of contact sensitization.

Conclusion

In this trial comparing the fentanyl placebo patch with a positive control (SLS) and a negative control (open unpatcehd area), the fentanyl placebo patch was found to be significantly less irritating than the SLS patch. There were no contact sensitization reactions noted in this study. The study did not include either the test or reference products. Since the active ingredient is contained within the adhesive of the generic transdermal, the placebo patch without fentanyl (adhesive only) is not comparable to the patch with the active ingredient (a single fentanyl-containing adhesive layer). Therefore, the observations in this study on skin irritation and contact sensitization potential cannot be extrapolated to the fentanyl generic transdermal system.

II. TITLE: A 21-Day, Randomized, Controlled Study to Evaluate the Local Tolerability of a Transdermal Delivery System for Fentanyl in Healthy Volunteers, using a Cumulative Irritant Patch Test Design (FENT-0133)

CRO: [redacted]

STUDY OBJECTIVE

The primary objective of this study was to determine the potential of the investigational transdermal delivery system for fentanyl to cause irritation after repeated topical application to the healthy skin of humans under controlled conditions. In addition, safety was assessed by evaluation of any adverse events reported during the study.

STUDY DESIGN

This was a randomized, single-center, controlled, within-subject comparative study of the test and positive and negative controls under occlusive conditions. Three test articles were compared:

1. Fentanyl Transdermal System Placebo (FTS), Lot #R6J0007, test article
2. Sodium Lauryl Sulfate (SLS), 0.2% aqueous solution; positive control
3. Saline, 0.9% solution; negative control

The study controls were evaluated under occlusive patch conditions by means of application of a [redacted] pad attached to a non-porous, plastic film adhesive bandage ([redacted]). The control patches were secured with hypoallergenic [redacted] tape as needed. A total of 15 applications were to be made over a period of 21 days. Scoring for irritation was done prior to re-application of a new patch and after removal of the last patch.

The analysis of mean cumulative irritation included all subjects with at least 1 post-baseline assessment. For discontinued subjects or missed evaluations, the last observation was carried forward (LOCF) to ensure that all subjects have 21 scores. Any site that was discontinued due to a limiting irritation was assigned a score of 3 until the end of the study. A total irritation score for each subject and product was calculated by summing each individual's scores on each of 15 evaluation days and adding 6 scores for Saturdays and Sundays equal to the score obtained the following Mondays.

Irritation scores were summarized by reading number using frequency distributions and descriptive statistics. These parameters were tested pairwise for product differences in the context of the 2-way analysis of variance (ANOVA). Pairwise differences were tested only if the null hypothesis of a common mean score for all products was rejected at the 5% level. A normalized total score for each patch was calculated by summing the total irritation scores for each subject. Products were compared with respect to the number of days until the patch was discontinued due to limiting irritation, using Friedman's test.

The study planned for enrollment of sufficient subjects to have 30 completed subjects. Patients who withdrew were not replaced.

STUDY CONDUCT

Forty-one subjects were enrolled in the study. Transdermal patches were applied to the upper back at the same site for the duration of the study unless the maximum allowable irritation limit was reached.

The primary measurement was the evaluation of irritation using a validated scoring system. Skin evaluations were conducted approximately 30 minutes after removal of the three patches by trained and blinded scorers. The following scale was used to quantify irritation:

0 = No visible reaction
0.5 = Papular or papulovesicular response and/or dryness without erythema
1 = Minimal or doubtful erythema (slightly different from surrounding normal skin)
1.5 = Minimal or doubtful erythema accompanied by papular or papulovesicular response and/or dryness
2 = Definite erythema
2.5 = Definite erythema accompanied by papular or papulovesicular response and/or dryness
3 = Definite erythema and definite edema with vesicles
3.5 = Definite edema with or without edema and severe damage to epidermis characterized by crusting, superficial erosions, or oozing

STUDY RESULTS

Cohort

Forty-one subjects were enrolled. The study report is dated September 6, 2001 but study dates could not be located in the submission. Six subjects were discontinued from the study. Five withdrew voluntarily and one refused to have control patches secured with hypoallergenic tape and was, therefore, considered a protocol violation. No one was discontinued because of adverse reactions.

Demographics

Thirty-four subjects (83%) were Caucasian, six Hispanic (15%) and one Asian (2%). Seven were male (17%) and 34 (83%) were female. The age distribution of the subjects was 20 to 60.

Adverse Events

Two subjects experienced 2 adverse events, dizziness and headache.

Mean Irritation Scores

The sponsor calculated the mean score for each evaluation day. A normalized mean total score was derived and the irritation characterized for all the patch types. These data are summarized in the table below (Table II). The Medical Officer's calculations of mean number of days until patch removal are also presented.

Table II
Mean Irritation Scores

Test Article	Mean Irritation	Normalized Total Score	#Discontinued due to Irritation	Mean # of Days to Patch Removal
Fentanyl	0.67 +/- 0.59	140	8	14.1
SLS	2.25 +/- 0.59	473	33	14.2
Saline	0.61 +/- 0.74	128	7	8.3

The Fentanyl transdermal system was significantly less irritating than the SLS control. It was comparable to the Saline control for mean irritation score and normalized mean total score. Thirty-three of the SLS patches had to be discontinued due to grade 3 irritation compared to 8 of the Fentanyl and 7 of the Saline patches. The SLS control led to significant and early irritation, with the average number of days until patch removal being 8.3, whereas the Fentanyl and Saline patches remained at the patch site for over 14 days. Based on pre-determined criteria, the Fentanyl and Saline patches were found to be slightly irritating and the SLS patch was characterized as highly irritating.

Distribution of Scores

The distribution of scores at each evaluation day is shown in Table III below. The Saline and Fentanyl patches had a similar pattern. However, the SLS patch led to irritation much earlier. By day 4, 28 subjects had a score of 2 at the SLS sites and 5 subjects had reached a score of 3. In contrast, 2 subjects first had a score of 3 at the Fentanyl site at day 9 and 3 subjects had scores of 3 at the saline site.

Table III

Proportion of subjects with individual scores of 0, 1+, 2+, and 3+ at evaluation times

Score	Day 1			Day 4			Day 9			Day 12			Day 15		
	F	SL	SA	F	SL	SA	F	SL	SA	F	SL	SA	F	SL	SA
0	38	34	37	32	0	35	17	0	19	11	0	17	9	0	13
1	0	4	1	4	3	1	13	0	6	13	0	6	11	0	5
2	0	0	0	0	28	0	3	4	7	4	2	7	5	2	9
3	0	0	0	0	5	0	2	31	3	7	33	5	10	33	8

Conclusion

This study compares the irritation potential of the fentanyl generic transdermal to that of two controls, one highly irritating and one of low irritation potential. While the fentanyl transdermal system is comparable to the saline control, this study does not provide information on the skin irritation potential of the generic product compared to its reference listed drug.

III. TITLE: Evaluation of Contact Sensitization Potential of Fentanyl Transdermal System in Normal Healthy Volunteers (FENT-0134)

CRO: [redacted]

STUDY OBJECTIVE

The objective of this study was to evaluate Mylan's fentanyl transdermal System (25 ug/hr), manufactured by Mylan Technologies, Inc., to Placebo Transdermal System for Mylan's product and the Innovator fentanyl transdermal system (Duragesic® 25 ug/hr, Janssen) in regards to induction of contact sensitization by repetitive applications to the skin of normal healthy, non-smoking adult volunteers. In addition, skin irritation and patch adherence will be monitored during the test system applications.

STUDY DESIGN

This was an open-label, parallel, two-group, single-center controlled study to evaluate the potential of contact sensitization of Mylan's fentanyl transdermal system as compared to placebo and Duragesic® in 28 healthy, non-smoking, adult volunteers.

Subjects were randomly assigned to one of the groups, A or B. Group A received the following treatments:

1. Fentanyl Transdermal System 25 ug/hr, Mylan Lot # R6J0001
2. Placebo Transdermal System, Mylan Lot # R6J0007.

Group B received the following treatment:

1. Duragesic ® Transdermal System 25 ug/mL, Janssen Lot # 9910472
2. An alternative open (untreated) site.

During the Induction period, the transdermal patches were applied 3 times a week for 48 hours except for Friday applications, which remained in place for 72 hours, for a total of 9 consecutive applications. Scoring for irritation was done prior to re-application of a new patch and after removal of the last patch. Any site reaching maximum irritation as defined below was not re-patched but it continued to be scored until the end of the study. In these cases, a patch was applied to an alternate site and scored as well for the remainder of the study. Naltraxone 50 mg twice a day, was started 24 hours prior to the first test system application and continued through the induction phase.

A two-week Rest period in which the subjects did not receive any application of test article ensued and was followed by a Challenge. One hundred mg of Naltraxone was administered for the first 4 days and the last day of this phase.

One 48-hour application of each test system to a naïve site was used to test for reactions indicative of contact sensitization. The sites were evaluated at 24, 48, and 72 hours post application. A re-challenge was carried out as appropriate and involved applying the test articles to a naïve site to confirm reactions indicative of contact sensitization.

Inclusion and exclusion criteria listed in the protocol were appropriate.

STUDY CONDUCT

Transdermal patches were applied to each subject's arm at the same site during the Induction phase of the study unless the maximum allowable irritation limit was reached (a score of > 3 or a letter grade of D, E, F, G, H, J, K, or N). Patches remained in contact with the skin for 48 +/- 5 hours following a Monday or Wednesday application or 72 +/- 5 hours following a Friday application.

The primary measurement for the Induction phase was the evaluation of skin irritation approximately 30 minutes following patch removal. Following the Induction phase, subjects did not receive any application of the test systems during a Rest period of 10 to 17 days. The Challenge application was made on Monday of the sixth week on the arm opposite to that used for the Induction phase.

Inflammatory responses associated with contact sensitization were scored using the following scales:

Dermal Response:

0 = No visible reaction or irritation
1 = Slight, confluent or patchy erythema
2 = Mild erythema; minimal edema or minimal papular response
3 = Moderate erythema (definite redness), papules and small blister
4 = Strong erythema (very intense redness), papules and small blister
5 = Marked swelling and blisters
6 = Vesicular eruption
7 = Strong reaction spreading beyond test site

Other effects:

A = slight glazed appearance
B = marked glazing
C = glazing with peeling and cracking
D = glazing with fissures
E = film of dried serous exudate covering all or part of the patch site
F = small petechial erosions and/or scabs
G = weeping as a result of vesicular or bulla reactions
H = solid, elevated, hardened, and thickened skin
J = hyperpigmentation (reddish-brown discoloration of test site)
K = hypopigmentation (loss of visible pigmentation at test site)
N = fissuring – grooves in the superficial layers of the skin

Applications during the Induction phase were terminated or moved to an adjacent site if a strong reaction was observed. The maximum limits allowed were as follows:

ANY numerical score that has been appended with a letter grade of D, E, F, G, H, J, K, or N

OR

Numerical score >3 regardless of the possible letter grade combination.

The letter grades were converted to numerical scores as follows: A = 0, B = 1, C = 2, and D, E, F, G, H, J, K, and N = 3. These numerical equivalents were considered additive to the numerical score (e.g., 2C = 2 + 2 = 4). They were added in the calculation of the total irritancy score for the entire cohort. The upper limit individual score selected was 3. All scores were calculated and those above this were entered as 3 in order to maintain the focus on evaluation of mild irritation expected for these products. Data from the test systems worn less than half of the required time were not utilized for the statistical analysis, unless a reaction occurred at the test site. A one-sided t-test comparing Mylan's generic to the innovator for cumulative irritation was performed.

A two-sided t-test was performed to test the differences between the placebo system and Mylan's fentanyl system for the same parameter. The mean irritation score per subject for each treatment was tested using the PROC GLM with treatment as the class variable. For the sensitization reactions, scoring at each site was done and a narrative provided by the observer as to whether this was a sensitization reaction or not.

Adhesion scores were also measured but were not the subject of this review. This study was intended to be a safety study and the pharmacokinetic profile of the subjects was also measured.

Concomitant medications and adverse events were recorded at each visit. The Investigator determined the severity and relatedness of adverse events to the test material.

STUDY RESULTS

The study was conducted between 5/31/01 and 7/08/01. Forty-three subjects were screened. Thirty-two subjects were enrolled and 28 subjects completed the study. Three subjects (# 30, 31 and 31) dropped out of the study for personal reasons not related to the study. Subject # 19 withdrew because of an adverse event, nausea and vomiting requiring IM phenergan treatment for 2 of the 6 episodes and abdominal cramping on 2 occasions. Thus, there were 14 evaluable subjects in each group.

Protocol deviations were primarily for concomitant medications. Six subjects received tylenol for headaches and one subject received IM Phenergan twice. All these deviations were with prior consultation with the Principal Investigator. One subject developed a grade 3B irritation and required patch movement. As this was the third move, the subject was re-patched at the site of the first move that had fully resolved at that time.

Demographics

Twenty-one (78%) subjects were Caucasian, ten (31%) were African American, and 1 (3%) was Hispanic. Seven (22%) were female and 25 (78%) were male. Subjects ranged in age from 19 to 49 years old.

Adverse Events

Seventeen subjects experienced 59 adverse events (ADEs). Of these, 26 were determined to have a Probable relationship to the study drug, 33 a Possible relationship, and 3 a Remote relationship. Forty-nine ADEs in 12 subjects were associated with the Duragesic® patch and 10 in 6 subjects with either the Fentanyl or the Mylan placebo patch. The frequency and type of adverse reactions are presented in the Table below (Table IV).

Table IV

Adverse Reactions Associated with Fentanyl, Placebo, and Duragesic® Transdermal Patches

Adverse Event	Probable	Possible	Mild	Moderate	Fentanyl	Duragesic
Headache	2	15	9	8	3	14
Vomiting	7	7	8	6	0	14
Nausea	8	2	8	2	4	6
Abdominal cramping	3	1	4	0	0	4
Muscle aches	0	3	3	0	1	2
Diarrhea	2	1	3	0	1	2
Sweating	2	1	3	0	0	3
Shakiness	1	1	2	0	1	1
Dizziness	1	0	1	0	0	1
Insomnia	0	2	2	0	0	2

Overall the Duragesic® patches were associated with more adverse events related to the active ingredient than the fentanyl patches. Other adverse events were experienced by 1 subject each and included a "lump in throat", yawning, runny nose, constipation, paleness, and muscle cramps.

Mean Irritation Scores

Mean irritation, mean total irritation, total cumulative irritation, and the number of days until patch removal were calculated for each patch (Table V).

Table V
Mean Irritation Scores

Test Article	Mean Irritation	Mean Total Irritation	Total Cumulative Irritation	Number Discontinued due to Irritation	Mean # of Days to Patch Removal
Fentanyl	0.30 +/- 0.41	2.9	40	0	21
Placebo	0.64 +/- 0.48	5.6	78	1	20.8
Duragesic	0.74 +/- 0.66	9.6	144	4	18

The Fentanyl generic was the least irritating of the three patches. The generic placebo was a bit more irritating that the same patch with fentanyl and the Duragesic patch was the most irritating of the three. The mean irritation of the fentanyl transdermal system and that of the Duragesic® transdermal systems were significantly different. The fentanyl generic and the placebo generic patch were significantly less irritating. However, the fentanyl generic was not significantly different from its placebo.

Adhesion

The sponsor provided an adhesion analysis that showed no significant differences among the three transdermal systems (Mylan's Fentanyl Transdermal System, Mylan's Placebo Transdermal System and Jansen's (innovator) Transdermal System) in adhesion.

Skin Sensitization

Two subjects had grade 2 reactions at the site of their patches at 30 minutes after patch removal. These reactions had resolved at the time of the 24-hour assessment and were not considered to be characteristic for a sensitization reaction. These were both with the Fentanyl generic transdermal system.

The sponsor measured the blood levels of fentanyl throughout the study. The results, appended to this review, show some tendency to higher levels with the Duragesic® patches between 14.5 and 16.7 days at a time when the irritation associated with this patch was high.

Conclusion

This study compared the Fentanyl generic transdermal system to the placebo transdermal in 14 subjects and the Duragesic® transdermal system to an open unpatched site in another 15 subjects. The Fentanyl generic was the least irritating of the three patches. The generic placebo was a bit more irritating than the same patch with active Fentanyl. The Duragesic patch was the most irritating of the three. The mean irritation of the fentanyl transdermal system and that of the Duragesic transdermal system differed significantly, according to the sponsor's analysis; the fentanyl generic was significantly less irritating. However, the generic patch without the active drug product in its adhesive matrix had a mean irritation score that approached that of the Duragesic® patch. The fentanyl generic was not significantly different from its placebo. Adverse events due to the active ingredient were more common in subjects who received the Duragesic® patches. There were no sensitization reactions in this study.

This study appears to be a pilot study with a very small sample size. These preliminary data suggest that Mylan's fentanyl transdermal system is less irritating than the Duragesic® transdermal system and to lead to fewer ADEs associated with the active drug product. It is plausible that the additional irritation noted with Duragesic® could lead to higher systemic levels of fentanyl and more frequent ADEs associated with the active ingredient. In this study, patches were applied for 48 hours twice a week and the labeled 72 hours once a week. This patching schedule is sufficiently close to the labeled use that the results can be extrapolated to the expected clinical use.

The observation that a generic transdermal is less irritating than the innovator product usually does not impact on the bioequivalence determination. The occurrence in this study of fewer ADEs due to the active ingredient in the generic product is presumably due to differences in drug absorption associated with observed differences in irritation potential. These adverse events are clinically important. Therefore, this observation suggests that the generic product is not bioequivalent from at least a safety point of view when chronically administered.

DISCUSSION

The sponsor has conducted 3 studies in normal human volunteers and none of them represent an ideal design to test for skin irritation and sensitization potential of the generic transdermal compared to its reference listed product.

In the first study (FENT-0132) comparing the fentanyl placebo patch with a positive control (SLS) and a negative control (open unpatcehd area), the fentanyl placebo patch was found to be significantly less irritating than the SLS patch. There were no contact sensitization reactions noted in this study. The study did not include either the test or reference products. Since the active ingredient is contained within the adhesive of the generic transdermal, the placebo patch without fentanyl (adhesive only) is not comparable to the patch with the active ingredient (a single fentanyl-containing adhesive layer). Therefore, the observations in this study on skin irritation and contact sensitization potential cannot be extrapolated to Mylan's fentanyl transdermal system.

The second study (FENT-0133) compared the irritation potential of the fentanyl generic transdermal to that of two controls, one highly irritating and one of low irritation potential in 35 subjects. While the fentanyl transdermal system is comparable to the saline control, this study does not provide information on the skin irritation potential of the generic product comparable to its reference listed drug.

The third study (FENT-0134) compared the Fentanyl generic transdermal system to the placebo transdermal in 14 subjects and the Duragesic® transdermal system to an open unpatched site in another 15 subjects. The Fentanyl generic was the least irritating of the three patches. The generic placebo was a bit more irritating than the same patch with active Fentanyl. The Duragesic patch was the most irritating of the three. The mean irritation of the fentanyl transdermal system and that of the Duragesic transdermal systems differed significantly, according to the sponsor's analysis. The fentanyl generic was significantly less irritating. However, the generic patch without the active drug product in its adhesive matrix had a mean irritation score that approached that of the Duragesic® patch. The fentanyl generic was not significantly different from its placebo. Adverse events due to the active ingredient were more common in subjects who received the Duragesic® patches. There were no sensitization reactions in this study.

This study appears to be a pilot study with a very small sample size. These preliminary data suggest that Mylan's fentanyl transdermal system is less irritating than the Duragesic® transdermal system and leads to fewer ADEs associated with the active drug product. In this study, patches were applied for 48 hours twice a week and the labeled duration of appliation (72) hours once a week. This patching schedule is sufficiently close to the labeled use that the results can be extrapolated to the expected clinical use.

The observation that a generic transdermal is less irritating than the innovator product usually does not impact on the bioequivalence determination. The occurrence in this study of fewer ADEs due to the active ingredient in the generic product is presumably due to differences in drug absorption associated with observed differences in irritation potential. These adverse events are clinically important. Therefore, this observation suggests that the generic product is not bioequivalent from at least a safety point of view when chronically administered.

In addition, the sponsor conducted 2 studies, one on irritation and a second on sensitization in animals. Animal studies do not have a part in establishing the relative safety of the generic and the reference listed drug. However, the recommended studies are to be conducted in humans. The required testing is outlined in the *Guidance for Industry: Skin Irritation and Sensitization Testing of Generic Transdermal Drug Products (12/99).*

This sponsor did not conduct a study that would comply with this guidance. Due, possibly, to concern over exposing normal volunteers to a potentially habituating drug (fentanyl), they used naltraxone blockade of the fentanyl effect. They appear to have been reluctant to the traditional design of applying 2 patches with active drug at the same time in a single patient. Therefore, instead of simultaneously testing the generic and reference listed drug in the same individual, they have chosen to conduct a small parallel group study comparing the two. Despite the small number of patients and because the Duragesic® patch is somewhat irritating, they have been able to demonstrate that the generic patch is less irritating than the reference listed drug and that neither cause sensitization. The study is too small to make any conclusions on the contact sensitization potential and the observed differences in skin irritation have not been analyzed by the FDA statistician.

Recommendation

The FENT-0134 study contains some pharmacokinetic data that should be reviewed the Division of Bioequivalence. In light of the marked difference in adverse events between the test and reference drug product, it is important to determine whether the systemic exposure and safety profile of the two active transdermal patches is indeed bioequivalent when used chronically or whether this product should be developed through a 505(b)(2) application.

The skin sensitization and irritation studies submitted by the sponsor are not adequate to characterize differences between the test vs. reference transdermal products. There is, however, some question as to whether these two products are bioequivalent from the point of view of safety.

The sponsor should be advised to conduct a new skin irritation/sensitization study using a parallel design and a sample size adequate to assess the potential for contact sensitization. This study should include a pharmacokinetic assessment of systemic exposure and a careful evaluation of adverse events.

Mary M. Fanning, M.D., Ph.D.
Associate Director of Medical Affairs
Office of Generic Drugs

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

76-258

CHEMISTRY REVIEW(S)

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Generic Drugs
Abbreviated New Drug Application Review

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1. **CHEMISTRY REVIEW NO.** 1

2. **ANDA #** 76-258

3. **NAME AND ADDRESS OF APPLICANT**
Mylan Technologies, Inc.
Attention: William E. Brochu
110 Lake Street
St. Albans, VT 05478
Phone: 802-527-7792
Fax: 802-527-0486

4. **LEGAL BASIS FOR SUBMISSION**
The basis for Mylan Technologies Inc.'s Fentanyl Transdermal Systems 25, 50, 75, and 100 µg/hr is RLD Duragesic®, NDA #019-813, held by Alza, which delivers Fentanyl 25, 50, 75, or 100 µg/hr for 3 days when applied to the skin.

US patent #4,588,580 expires on 7/23/04. Updated Paragraph IV patent certification is provided on pp. 8, 12/4/01. There is no unexpired exclusivity for this drug product.

5. **SUPPLEMENT(s)**
N/A

6. **PROPRIETARY NAME**
N/A

7. **NONPROPRIETARY NAME**
Fentanyl

8. **SUPPLEMENT(s) PROVIDE(s) FOR:**
N/A

9. **AMENDMENTS AND OTHER DATES:**
Firm:
10/12/01 - Original Submission
12/4/01 - Major Amendment

FDA:
11/26/01 - Receipt Acknowledged

10. **PHARMACOLOGICAL CATEGORY**
Management of chronic pain in patients requiring opioid analgesia

11. **Rx or OTC**: Rx

12. **RELATED IND/NDA/DMF(s)**

DMF #
DMF #
DMF #
DMF #
DMF #
DMF #
DMF #

13. **DOSAGE FORM**

Transdermal Patch

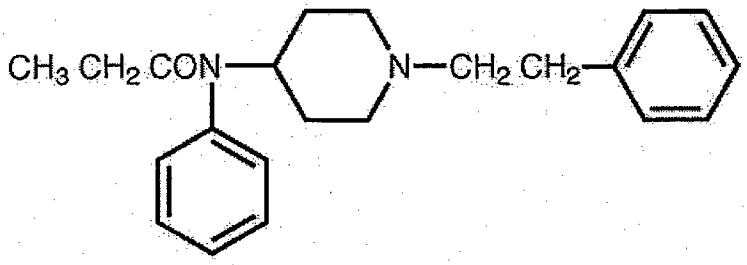
14. **POTENCIES**

25, 50, 75, and 100 µg/hr

15. **CHEMICAL NAME AND STRUCTURE**

Fentanyl

Formula: $C_{22}H_{28}N_2O$; M.W.: 336.5



Chemical Name:

1. N-Phenyl-N-[1-(2-phenylethyl)-4-piperidyl]propanamide
2. N-(1-Phenethyl-4-piperidyl)propionanilide

16. **RECORDS AND REPORTS**

17. **COMMENTS**

Both drug substance and drug product are not compendial.
Method validation will be requested.

EER result is pending.
DMF # —— is inadequate, 1/23/02.
Labeling review is pending.
Bioequivalence review is pending.
Pharm-Tox consult was requested; result is pending.

18. **CONCLUSIONS AND RECOMMENDATIONS**

Not Approvable - Minor

19. **REVIEWER:** Tao-Chin L. Wang

DATE COMPLETED: 1/31/02

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Center for Drug Evaluation and Research
Office of Generic Drugs
Abbreviated New Drug Application Review

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1. **CHEMISTRY REVIEW NO.** 2

2. **ANDA #** 76-258

3. **NAME AND ADDRESS OF APPLICANT**
Mylan Technologies, Inc.
Attention: William E. Brochu
110 Lake Street
St. Albans, VT 05478
Phone: 802-527-7792 x426
Fax: 802-527-8155

4. **LEGAL BASIS FOR SUBMISSION**
The basis for Mylan Technologies Inc.'s Fentanyl Transdermal Systems 25, 50, 75, and 100 µg/hr is RLD Duragesic®, NDA #019-813, held by Alza, which delivers Fentanyl 25, 50, 75, or 100 µg/hr for 3 days when applied to the skin.

US patent #4,588,580 expires on 7/23/04. Updated Paragraph IV patent certification is provided on pp. 8, 12/4/01. There is no unexpired exclusivity for this drug product.

5. **SUPPLEMENT(s)**
N/A

6. **PROPRIETARY NAME**
N/A

7. **NONPROPRIETARY NAME**
Fentanyl

8. **SUPPLEMENT(s) PROVIDE(s) FOR:**
N/A

9. **AMENDMENTS AND OTHER DATES:**
Firm:

10/12/01 -	Original Submission
12/4/01 -	Major Amendment
5/13/02, 6/21/02 -	Control Correspondence
6/11/02 -	Patent Amendment
6/20/02 -	Minor Amendment
7/31/02 -	Amendment
8/7/02 -	Label Amendment
10/14/02 -	Bio Amendment

FDA:
11/26/01 - Receipt Acknowledged
4/15/02 - Deficiency Letter

10. **PHARMACOLOGICAL CATEGORY**
Management of chronic pain in patients requiring opioid analgesia

11. **Rx or OTC**:
Rx

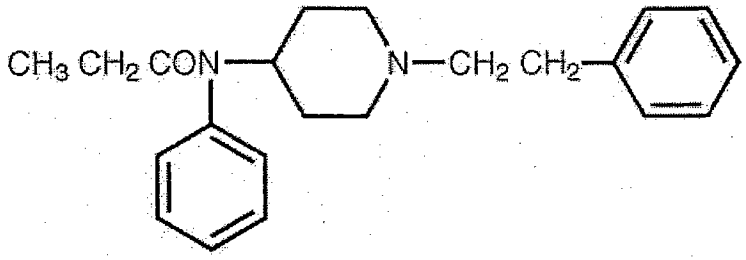
12. **RELATED IND/NDA/DMF(s)**
DMF
DMF
DMF
DMF
DMF #
DMF #
DMF #

13. **DOSAGE FORM**
Transdermal Patch

14. **POTENCIES**
25, 50, 75, and 100 µg/hr

15. **CHEMICAL NAME AND STRUCTURE**

Fentanyl
Formula: $C_{22}H_{28}N_2O$; M.W.: 336.5



Chemical Name:
1. N-Phenyl-N-[1-(2-phenylethyl)-4-piperidyl]propanamide
2. N-(1-Phenethyl-4-piperidyl)propionanilide

16. **RECORDS AND REPORTS**
Medical Officer Review - 1/24/01
Medical Officer Memo - 8/15/02
Labeling Review - 8/26/02

17. **COMMENTS**

Both drug substance and drug product are not compendial. Method validation was submitted on 5/30/02.

EER was submitted. Withhold recommendation was issued for the [redacted] 2/6/02.

DMF [redacted] is inadequate, 9/27/02.
Labeling is satisfactory, 8/26/02.
Bioequivalence review is pending.

Pharma-tox consult for [redacted] has been submitted. Result is acceptable.

18. **CONCLUSIONS AND RECOMMENDATIONS**

Not Approvable - Minor Amendment

19. **REVIEWER:** Tao-Chin L. Wang **DATE COMPLETED:** 9/30/02

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1. **CHEMISTRY REVIEW NO.** 3

2. **ANDA** # 76-258

3. **NAME AND ADDRESS OF APPLICANT**
Mylan Technologies, Inc.
110 Lake Street
St. Albans, VT 05478
Phone: 802-527-7792 x426
Fax: 802-527-8155

4. **LEGAL BASIS FOR SUBMISSION**
The basis for Mylan Technologies Inc.'s Fentanyl Transdermal Systems 25, 50, 75, and 100 μg/hr is the RLD, Duragesic® (NDA #019-813), held by Alza, which delivers Fentanyl 25, 50, 75, or 100 μg/hr for 3 days when applied to the skin.

US patent #4,588,580 expires on 7/23/04. Paragraph IV patent certification is updated and provided on pp. 8, 12/4/01. There is no unexpired exclusivity for this drug product.

5. **SUPPLEMENT(s)**
N/A

6. **PROPRIETARY NAME**
N/A

7. **NONPROPRIETARY NAME**
Fentanyl

8. **SUPPLEMENT(s) PROVIDE(s) FOR:**
N/A

9. **AMENDMENTS AND OTHER DATES:**

Firm:

10/12/01 -	Original Submission
12/4/01 -	Major Amendment
5/13/02, 6/21/02 -	Control Correspondence
6/11/02 -	Patent Amendment
6/20/02 -	Minor Amendment
7/31/02 -	Amendment
11/20/02 -	Minor Amendment

FDA:

11/26/01 -	Receipt Acknowledged
4/15/02 -	Deficiency Letter
11/05/02 -	Deficiency Letter

10. **PHARMACOLOGICAL CATEGORY**
Management of chronic pain in patients requiring continuous opioid analgesia for pain

11. **Rx or OTC**:
Rx

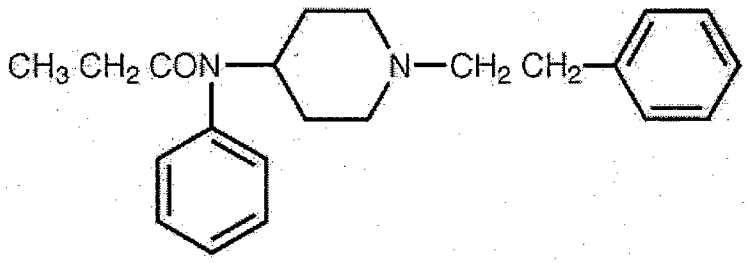
12. **RELATED IND/NDA/DMF(s)**
DMF #
DMF #
DMF #
DMF #
DMF #
DMF #
DMF #

13. **DOSAGE FORM**
Transdermal Patch

14. **POTENCIES**
25, 50, 75, and 100 μg/hr

15. **CHEMICAL NAME AND STRUCTURE**

Fentanyl
Formula: $C_{22}H_{28}N_2O$; M.W.: 336.5



Chemical Name:
1. N-Phenyl-N-[1-(2-phenylethyl)-4-piperidyl]propanamide
2. N-(1-Phenethyl-4-piperidyl)propionanilide

16. **RECORDS AND REPORTS**
Medical Officer Review – 1/24/01
Medical Officer Memo – 8/15/02
Labeling Review – 8/26/02
Bio Review – 1/24/03

17. **COMMENTS**
Both drug substance and drug product are not compendial. Method validation was submitted on 5/30/02.

EER was submitted 3/27/03.

DMF # ———adequate, 2/24/03.
Labeling is satisfactory, 8/26/02.

Bioequivalency amendment submitted on 10/14/02 was reviewed and found acceptable. Bioequivalence is satisfactory, 1/24/03. However, the firm submitted another bioequivalency amendment on 12/20/02. The amendment is pending review.

Pharma-tox consult was requested. Clinical studies FENT-0132 and FENT-0133 concluded that the use of Mylan's Fentanyl Transdermal System is unlikely to result in a degree of skin irritation or sensitization that is greater than that seen with the use of the reference product, Duragesic® Transdermal System (bioequivalence review 1/24/03).

18. **CONCLUSIONS AND RECOMMENDATIONS**
Not Approvable – Minor Amendment

19. **REVIEWER:** Tao-Chin L. Wang

DATE COMPLETED: 2/25/03

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Food and Drug Administration
Center for Drug Evaluation and Research
Office of Generic Drugs
Abbreviated New Drug Application Review

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1. **CHEMISTRY REVIEW NO.** 4

2. **ANDA #** 76-258

3. **NAME AND ADDRESS OF APPLICANT**
Mylan Technologies, Inc.
110 Lake Street
St. Albans, VT 05478
Phone: 802-527-7792 x426
Fax: 802-527-8155

4. **LEGAL BASIS FOR SUBMISSION**
The basis for Mylan Technologies Inc.'s Fentanyl Transdermal Systems 25, 50, 75, and 100 μg/hr is the RLD, Duragesic® (NDA #019-813), held by Alza, which delivers Fentanyl 25, 50, 75, or 100 μg/hr for 3 days when applied to the skin.

US patent #4,588,580 expires on 7/23/04. Paragraph IV patent certification is updated and provided on pp. 8, 12/4/01. There is no unexpired exclusivity for this drug product.

5. **SUPPLEMENT(s)**
N/A

6. **PROPRIETARY NAME**
N/A

7. **NONPROPRIETARY NAME**
Fentanyl

8. **SUPPLEMENT(s) PROVIDE(s) FOR:**
N/A

9. **AMENDMENTS AND OTHER DATES:**

Firm:

10/12/01 -	Original Submission
12/4/01 -	Major Amendment
5/13/02, 6/21/02 -	Control Correspondence
6/11/02 -	Patent Amendment
6/20/02 -	Minor Amendment
7/31/02 -	Amendment
11/20/02 -	Minor Amendment
04/05/03	Minor amendment
07/27/03	Minor amendment

FDA:

11/26/01 -	Receipt Acknowledged
4/15/02 -	Deficiency Letter
11/05/02 -	Deficiency Letter

10. **PHARMACOLOGICAL CATEGORY**
Management of chronic pain in patients requiring continuous opioid analgesia for pain

11. **Rx or OTC**:
Rx

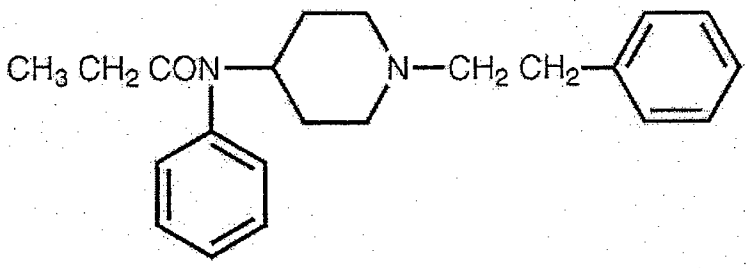
12. **RELATED IND/NDA/DMF(s)**
DMF #
DMF #
DMF #
DMF #
DMF #
DMF #
DMF #

13. **DOSAGE FORM**
Transdermal Patch

14. **POTENCIES**
25, 50, 75, and 100 μg/hr

15. **CHEMICAL NAME AND STRUCTURE**

Fentanyl
Formula: $C_{22}H_{28}N_2O$; M.W.: 336.5



Chemical Name:
1. N-Phenyl-N-[1-(2-phenylethyl)-4-piperidyl]propanamide
2. N-(1-Phenethyl-4-piperidyl)propionanilide

16. **RECORDS AND REPORTS**
Medical Officer Review – 1/24/01
Medical Officer Memo – 8/15/02
Labeling Review – 8/26/02
Bio Review – 1/24/03

17. **COMMENTS**
Both drug substance and drug product are not compendial. Method validation was submitted on 5/30/02.

EER was submitted 3/27/03.

DMF # ——— is adequate, 2/24/03.
Labeling is satisfactory, 8/26/02.

Bioequivalency amendment submitted on 10/14/02 was reviewed and found acceptable. Bioequivalence is satisfactory 1/24/03.

Pharma-tox consult was requested. Clinical studies FENT-0132 and FENT-0133 concluded that the use of Mylan's Fentanyl Transdermal System is unlikely to result in a degree of skin irritation or sensitization that is greater than that seen with the use of the reference product, Duragesic® Transdermal System (bioequivalence review 1/24/03).

18. **CONCLUSIONS AND RECOMMENDATIONS**
Approvable.

19. **REVIEWER:** A.Langowski

DATE COMPLETED: 07/17/03

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ADDENDUM

ANDA # 76-258 REVIEW # 4

NAME AND ADDRESS OF APPLICANT
Mylan Technologies, Inc.
110 Lake Street
St. Albans, VT 05478

PROPRIETARY NAME	NONPROPRIETARY NAME
N/A	Fentanyl Transdermal System

AMENDMENT DATE: October 24, 2003

COMMENTS
Per telephone request, the firm submitted justification for the viscosity specification for the solvated adhesive. The firm noted that the viscosity specification has been revised from [redacted] cps to [redacted] cps. Note that the innovator drug product uses a similar adhesive and the new specification is consistent with that for the RLD.

As part of the justification, the firm submitted a graph of viscosity versus solid content and a table showing the relationship of viscosity to finished product specifications regarding adhesive properties of the transdermal patch. The data submitted appear to support the new specification.

CONCLUSIONS AND RECOMMENDATIONS
The application be be approved.

REVIEWER:
Glen Jon Smith
Team Leader

DATE COMPLETED:
October 28, 2003

10/28/03

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

76-258

BIOEQUIVALENCE REVIEW(S)

BIOEQUIVALENCY DEFICIENCIES

ANDA/AADA: 76-258 APPLICANT: Mylan Technologies, Inc.

DRUG PRODUCT: FENTANYL TRANSDERMAL PATCH 25 mcg/hr

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiencies have been identified:

1. You have conducted 3 studies and none of them represent an ideal design to test for skin irritation and sensitization potential of the generic transdermal compared to its reference listed product.

In the first study (FENT-0132) comparing the fentanyl placebo patch with a positive control (SLS) and a negative control, the placebo patch was found to be significant less irritating the SLS patch. There were no contact sensitization reactions noted in this study. The study did not include either the test or reference products. Since the active ingredient is contained within the adhesive of the generic transdermal, the placebo patch without fentanyl is not comparable to the patch with the active ingredient. Therefore, the observations in this study on skin irritation and contact sensitization potential cannot be extrapolated to Mylan's transdermal system.

In the second study (FENT-0133) comparing the irritation potential of the fentanyl generic transdermal to that of two controls, the fentanyl system is comparable to the saline control, but this study does not provide information on the skin irritation potential of the generic product comparable to its reference listed drug.

The third study (FENT-0134) compared the fentanyl generic transdermal system to the placebo transdermal system in 14 subjects and the Duragesic transdermal system to an open unpatched site in another 15 subjects. The fentanyl generic was the least irritating of the three patches, and the generic placebo was a bit more irritating than the same patch with active fentanyl. The Duragesic patch was the most irritating of the three, and the fentanyl generic was significantly less irritating. However, the generic patch without the active drug product in its adhesive matrix had a mean irritation

score that approached that of the Duragesic patch. The fentanyl generic was not significantly different from its placebo. There were no sensitization reactions in this study. This study appears to be a pilot study with a very small sample size. These preliminary data suggest that Mylan's fentanyl transdermal system is less irritating than the Duragesic transdermal system and leads to fewer ADEs associated with the active product. Therefore, this observation suggests that the generic product is not equivalent from at least a safety point of view when chronically administered.

In addition, you conducted two studies, one on irritation and a second on sensitization in animals. However, the recommended studies are to be conducted in humans. The required testing is outlined in the guidance: *Guidance for Industry: Skin Irritation and Sensitization Testing of Generic Transdermal Drug Products, December 1999.*

You did not conduct the studies that are recommended in the guidance. Due, possibly, to concern over exposing normal volunteers to a potentially habituating drug (fentanyl), you have used naltraxone blockade of the fentanyl effect. You appeared to have been reluctant to use the traditional design of applying 2 patches with active drug at the same time in a single patient. Therefore, instead of simultaneously testing the generic and reference listed drug in the same individual, you have chosen to conduct a small parallel group study comparing the two. Despite the small number of patients and because the Duragesic® patch is somewhat irritating, you have been able to demonstrate that the generic patch is less irritating than the reference listed drug and that neither cause sensitization. The study is too small to make any conclusions on the contact sensitization potential and the observed differences in skin irritation have not been analyzed by the FDA statistician.
Hence, studies on assessing skin irritation and sensitization and patch adhesion are incomplete. You are requested to submit a new skin irritation/sensitization study using a parallel design and a sample size adequate to assess the potential for contact sensitization, for evaluation. Please refer to the Agency's guidance: *Guidance for Industry: Skin Irritation and Sensitization Testing of Generic Transdermal Drug Products, December 1999* for more information. This guidance is available on the internet at: http://www.fda.gov/cder/guidance/index.htm

2. The dissolution testing data is incomplete. You are requested to conduct dissolution testing on 12 individual dosage units for the test and reference products. Dissolution testing should be conducted in different media ([redacted] and multipoint dissolution profiles should be obtained using discriminating agitation speed. A surfactant may be used with appropriate justification. Adequate sampling times should be performed (See current USP Sections <711> and <724> for general dissolution requirements).

3. Please indicate how [redacted] was prepared. The USP indicates that pH of the [redacted] cannot go below [redacted] See USP 24 page 2232).

4. Study FENT-0134 contains some pharmacokinetic data. In order to evaluate those data, you are requested to calculate appropriate pharmacokinetic parameters and statistically compare PK parameters of the test and RLD.

5. Please submit all analytical SOPs including the one for sample repeats.

Sincerely yours,

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

JAN 24 2003

Fentanyl Transdermal System
25 μg/h
ANDA 76-258
Reviewer: Nhan L. Tran
V:\firmsam\mylan\ltrs&rev\76258A1002.doc

Mylan Technologies
St. Albans, VT 05478
Submission date:
October 14, 2002

Review of an Amendment

BACKGROUND

The firm submitted the original submission on 10/12/2001 and it was reviewed on 4/8/2002. Several deficiencies were listed in the review and the firm is responding to those deficiencies.

REVIEW OF THE RESPONSES

Deficiency 1: Data on assessing skin irritation/sensitization and patch adhesion are incomplete. The firm is requested to submit a new skin irritation/sensitization study to assess the potential for contact sensitization.

Firm's Response: The firm has requested the Agency to reconsider its position on the need of new irritation/sensitization and patch adhesion studies.

FDA comment: The Medical Reviewer has reviewed the response and concluded that studies FENT-0132 and FENT-0133, along with the literature overview of dermatological reactions produced by transdermal fentanyl, are adequate to demonstrate that use of Mylan's Fentanyl Transdermal System is unlikely to result in a degree of skin irritation or sensitization that is greater than that seen with use of the reference product Duragesic® Transdermal System. The OGD's Medical Reviewer decided that no new study will be needed.
The firm's response is acceptable.

Deficiency 2: Study FENT-0134 contains some pharmacokinetic data. In order to evaluate those data, the firm is requested to calculate appropriate pharmacokinetic parameters and statistically compared PK parameters of the test and RLD.

Firm's response: Study FENT-0134 was not designed to make inferences of bioequivalence, and hence data from this study are not appropriate for calculation of pharmacokinetic parameters and statistical comparisons of pharmacokinetics for the test and reference products.

FDA's comment: After further review of study FENT-0134, the Medical Reviewer concurred with the firm that further information about pharmacokinetic data from that study was not needed.

The firm's response is acceptable.

Deficiency 3: The firm is requested to conduct dissolution testing on 12 individual dosage units for the test and reference products. Dissolution testing should be conducted in different media ([redacted] and multipoint dissolution profiles should be obtained using discriminating agitation speed. A surfactant may be used with appropriate justification.

Firm's Response: The firm submitted the following dissolution data:

1. Dissolution test in different media

The firm has conducted dissolution testing in different media as follows:

STRENGTH: 25 mcg/hr
ANALYTE: FENTANYL
MEDIUM: [redacted]
VOLUME: [redacted]
APPARATUS: [redacted]
RPM: [redacted]
ASSAY METHOD: [redacted]

Results are shown in table below, with a mean of 6 dosage units along with %CV:

Time (hrs)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
0.5	29 (4.2)	30 (5.5)	30 (3.4)	21 (1.9)	15 (6)	15 (6)
1	43 (3.6)	46 (4.3)	45 (1.8)	34 (1.2)	29 (3.6)	26 (8.2)
2	62 (2.1)	65 (3.4)	66 (1.3)	52 (1.2)	43 (2.8)	43 (7.4)
4	85 (2.3)	87 (2.8)	88 (1.4)	70 (1.5)	57 (2.4)	65 (5.5)
8	97 (1.2)	99 (1.8)	99 (0.9)	78 (1.4)	60 (1.6)	77 (4.5)
24	104 (0.7)	104 (1.3)	103 (0.7)	70 (2.5)	43 (1.5)	76 (2.8)
32				65 (1.9)		74 (2.2)

The results indicated that:

- Similar release rate for [redacted]
- The release rate was slower in [redacted]

2. Dissolution test with varying rotation speeds

The firm has conducted dissolution testing using [redacted] with varying paddle speed as follows:

STRENGTH: 25 mcg/hr
ANALYTE: FENTANYL
MEDIUM: [redacted]
VOLUME: [redacted]
APPARATUS: [redacted]

RPM:
ASSAY METHOD:

Results are shown in table below, with a mean of 6 dosage units along with %CV:

Sampling time	Drug Release as % of Label claim (%CV, N=6)		
(hrs)			
0.5	29 (3.6)	30 (5.7)	30 (4.4)
1	44 (3.3)	46 (4.3)	44 (2.9)
2	64 (2.1)	65 (3.5)	65 (4.4)
4	86 (1.8)	87 (2.7)	86 (2.5)
8	98 (1.9)	99 (1.9)	99 (1.6)
24	103 (2)	104 (1.3)	104 (0.9)

The release rates were virtually the same regardless of paddle speeds.

3. Dissolution profiles of all strengths using the following conditions:

STRENGTHS: 25, 50, 75 and 100 mcg/hr
ANALYTE: FENTANYL
MEDIUM:
VOLUME:
APPARATUS:
RPM:
ASSAY METHOD:

Results are shown in table below, with a mean of 12 dosage units along with %CV:

RESULTS OF DISSOLUTION TESTING: 25 mcg/hr								
Time(hour)	0.5		1		2		8	
	R6J0001 (Test)	9910472 (Ref)	R6J0001 (Test)	9910472 (Ref)	R6J0001 (Test)	9910472 (Ref)	R6J0001 (Test)	9910472 (Ref)
MEAN	**29.50**	**15.08**	**44.17**	**18.58**	**63.67**	**22.58**	**97.50**	**38.42**
CV%	3.39	5.26	3.46	2.77	3.56	2.96	2.03	3.41
MIN								
MAX								

RESULTS OF DISSOLUTION TESTING: 50 mcg/hr								
Time(hour)	0.5		1		2		8	
	R6J0011 (Test)	0109258 (Ref)	R6J0011 (Test)	0109258 (Ref)	R6J0011 (Test)	0109258 (Ref)	R6J0011 (Test)	0109258 (Ref)
MEAN	**28**	**10**	**43**	**12**	**62**	**15**	**93**	**28**
CV%	2.1	4	2.5	2	1.4	3.5	0.6	3.8
MIN								
MAX								

RESULTS OF DISSOLUTION TESTING: 75 mcg/hr								
Time(hour)	0.5		1		2		8	
	R6J0010 (Test)	0108818 (Ref)	R6J0010 (Test)	0108818 (Ref)	R6J0010 (Test)	0108818 (Ref)	R6J0010 (Test)	0108818 (Ref)
MEAN	**28**	**9**	**43**	**12**	**63**	**14**	**96**	**26**
CV%	5.2	4.9	4	4.8	2.8	4.4	1.6	5.4
MIN	[redacted]							
MAX								

RESULTS OF DISSOLUTION TESTING: 100 mcg/hr								
Time(hour)	0.5		1		2		8	
	R6J0008 (Test)	9910192 (Ref)	R6J0008 (Test)	9910192 (Ref)	R6J0008 (Test)	9910192 (Ref)	R6J0008 (Test)	9910192 (Ref)
MEAN	**28**	**10**	**45**	**13**	**63**	**15**	**92**	**26**
CV%	2.2	6.4	1.7	6.5	1	6.4	1.6	6.8
MIN	[redacted]							
MAX								

FDA's comment: Dissolution data provided by the firm indicated that for its FTS, the optimum pH should be below [redacted] and the rotation speed of [redacted] appeared to be adequate for release testing. There exists a difference in the release rates of the test and RLD formulations. The difference may be due to different release characteristics of the two formulations.
Dissolution data is acceptable.

Deficiency 4: Please indicate how [redacted] was prepared. The USP indicates that pH of the [redacted] cannot go below [redacted] See USP 24 page 2232).

Firm's Response: Buffer was prepared by dissolving [redacted] and adjusted to [redacted]

FDA's comment: The response is acceptable.

Deficiency 5: Firm should submit all analytical SOPs including the one for sample repeats.

Firm's Response: Requested information was submitted.

FDA's comment: The information was reviewed and acceptable.

RECOMMENDATIONS:

1. The bioequivalence study #FENT-0105 conducted by Mylan Technologies, on its Fentanyl Transdermal System, 25 mcg/hr, lot #R6J0001, comparing it to Duragesic® manufactured by Janssen Pharmaceutical, has been found acceptable by the Division of Bioequivalence. The study demonstrates that Mylan Technologies'

Fentanyl Transdermal System, 25 mcg/hr, is bioequivalent to the reference product Duragesic® 25 mcg/hr, manufactured by Janssen Pharmaceutical.

2. Clinical studies FENT-0132 and FENT-0133 conducted by Mylan Technologies to assess the skin irritation/sensitization are acceptable. The studies are adequate to demonstrate that the use of Mylan's Fentanyl Transdermal System is unlikely to result in a degree of skin irritation or sensitization that is greater than that seen with the use of the reference product, Duragesic® Transdermal System.

3. The *in vitro* drug release testing conducted by Mylan Technologies, on its Fentanyl Transdermal System, 25 mcg/hr, lot #R6J0001, is acceptable. The dissolution testing should be conducted in [redacted] The test product should meet the following specifications:

   0.5 Hr: [redacted]
   1 Hr: [redacted]
   2 Hrs: [redacted]
   8 Hrs: NLT [redacted]

Nhan L. Tran, Ph.D. 1/22
Review Branch II

RD INITIALLED SNERURKAR
FT INITIALLED SNERURKAR 1/22/2003

Concur: Dale P. Conner Date: 1/24/03
Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence

CC: ANDA 76-258 (original), HFD 655 (Tran, Nerurkar), Drug File, Division File

APPEARS THIS WAY
ON ORIGINAL

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA/AADA: 76-258 APPLICANT: Mylan Technologies, Inc.

DRUG PRODUCT: FENTANYL TRANSDERMAL PATCH 25 mcg/hr

The Division of Bioequivalence has completed its review and has no further questions at this time.

We acknowledge that the following dissolution testing has been incorporated into your stability and quality control programs: The dissolution testing should be conducted in [redacted] The test product should meet the following specifications:

0.5 Hr: [redacted]
1 Hr: [redacted]
2 Hrs: [redacted]
8 Hrs: NLT [redacted]

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

CC: ANDA
ANDA DUPLICATE
DIVISION FILE
FIELD COPY
DRUG FILE

Endorsements: (Final with Dates)
HFD-655/Reviewer 1/22/03
HFD-655/Bio Team Leader
HFD-617/Project Manager
HFD-650/Dale Conner 1/24/03

BIOEQUIVALENCY - ACCEPTABLE

Submission Date:
October 14, 2002

1. **STUDY AMENDMENT** (STA)

Strengths: 25 mcg/hr
Outcome: AC

Outcome Decisions:

Acceptable

WinBio Comments

APPEARS THIS WAY
ON ORIGINAL

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA #: 76-258	SPONSOR: Mylan Technologies
DRUG	Fentanyl
DOSAGE FORM	Transdermal Patch
STRENGTHS	25 mcg/hr
TYPES OF STUDY	Fasting *In Vivo* Bioequivalence study and skin irritation/ sensitization studies (clinical).
CLINICAL STUDY SITES	[redacted]
ANALYTICAL SITE	[redacted]

STUDY SUMMARY	Fasting *In-Vivo* Bioequivalence Study and clinical studies (skin irritation/sensitization) are acceptable.
DISSOLUTION	Acceptable

DSI INSPECTION STATUS

Inspection needed: No	Inspection status:	Inspection results: [redacted]
First Generic Yes New facility No	Inspection requested: (date) Inspection completed: (date)	

PRIMARY REVIEWER: Nhan L. Tran, Ph.D. BRANCH: II

INITIAL: _____ DATE: 1/22

TEAM LEADER: S. Nerurkar, Ph.D. BRANCH: II

INITIAL: _____ DATE: 1/22/2003

DIRECTOR, DIVISION OF BIOEQUIVALENCE: Dale P. Conner, Pharm. D.

INITIAL: _____ DATE: 1/24/03

APPEARS THIS WAY
ON ORIGINAL

ANDA 76-258
CD 02-369
P 02-026

Drug Product:	**Fentanyl Transdermal System 25 μg/hr**
Sponsor:	**Mylan Technologies, Inc.**
Reference Listed Drug:	**Duragesic Transdermal System, Janssen Pharmaceuticals**
Date of submission:	**May 13, 2002**
Date of CD:	**June 21, 2002**
Date of review:	**September 18, 2002**
Reviewer:	**Dena R. Hixon, M.D.** **Associate Director for Medical Affairs**

Background

Fentanyl Transdermal System provides continuous systemic delivery of fentanyl, a potent opioid analgesic, for 72 hours. It is indicated for the management of chronic pain that cannot be managed by lesser means.

Mylan Technologies, Inc. submitted ANDA 76-258 for Fentanyl Transdermal System on October 12, 2001. The Mylan system differs from the reference product in that the delivery system for the reference product includes a drug reservoir with a membrane that controls the rate of delivery of fentanyl to the skin surface, while the Mylan product contains a fentanyl-silicone adhesive matrix layer. A bioequivalence review found the in-vivo bioequivalence study acceptable.

The application included five studies assessing skin irritation and sensitization. Two of these studies were animal studies and were not reviewed by the medical officer. The following three human studies were reviewed and found to be inadequate to compare the generic product to the reference product.

1. FENT-0132 "A Randomized, Controlled Study to Evaluate the Sensitizing Potential of a Transdermal Delivery System for Fentanyl in Healthy Volunteers, Using a Human Repeat Insult Patch Test Design" was a randomized controlled within-subject comparison to evaluate the potential for induction of contact sensitization and irritation with use of Mylan's system compared to a positive and negative control. The study enrolled 230 subjects, of which 202 were included in the final analysis. Each subject received a placebo patch (identical to the fentanyl transdermal system except for the absence of fentanyl), a positive control patch of sodium lauryl sulfate (SLS) 0.1% aqueous solution applied under occlusive patch conditions, and an open unpatched area as a negative control. The patches were applied to the same skin site three times per week for a total of 9 consecutive applications, and skin irritation was evaluated with a standard scoring system at each patch change. After a 2-week patch-free interval, a 48-hour application of each system to a naïve site was used to test for reactions indicative of contact sensitization.

The fentanyl placebo patch was found to be less irritating that the SLS, and the SLS led to sufficient irritation to require patch removal much more frequently and much earlier in the study than did the generic placebo. No contact sensitization reactions were noted. The reviewer concluded that the observations in this study on skin irritation and contact sensitization potential cannot be extrapolated to the fentanyl generic transdermal system because the active ingredient is contained within the adhesive of the generic transdermal system.

2. FENT-0133: "A 21-day, Randomized, Controlled Study to Evaluate the Local Tolerability of a Transdermal Delivery System for Fentanyl in Healthy Volunteers, Using a Cumulative Irritant Patch Test Design" was a randomized controlled within-subject comparative study of the test and positive and negative controls under occlusive conditions. The study enrolled 41 subjects, and 35 subjects were included in the analysis. They each received a fentanyl transdermal system placebo, a positive control of sodium lauryl sulfate (SLS) 0.2% aqueous solution, and a negative control of saline, 0.9%. Mean and cumulative total irritation scores were calculated using a standard scoring system.

   The placebo patch was less irritating than the SLS control and was comparable to the saline control for mean irritation score. The SLS produced significant and early irritation, and 33 of the SLS patches had to be discontinued due to grade 3 irritation. The reviewer concluded that this study does not provide comparative information on the skin irritation potential of the generic product compared to its reference listed drug.

3. FENT-0134: "Evaluation of contact sensitization potential of Fentanyl Transdermal System in Normal Healthy Volunteers" was an open-label parallel, two-group controlled study in which 42 subjects (28 evaluable) were randomized to receive either one Fentanyl Transdermal System 25 μg/hr and one placebo transdermal system or one Duragesic® Transdermal System 25 μg/hr and an alternative open (unpatched) site. Patches were applied 3 times a week for 48 to 72 hours, for a total of 9 consecutive applications to the same site. Naltrexone 50 mg twice a day was started 24 hours prior to the first test system application and continued through the induction phase. Scoring for irritation was performed at each patch change. Following a two-week rest, another patch was applied to a naïve site for 48 hours (along with Naltrexone 100 mg/day for 4 days) to test for sensitization reactions.

   The Fentanyl generic was the least irritating of the 3 patches, and the Duragesic® patch was the most irritating. There were no sensitization reactions. The sponsor's adhesion analysis showed no significant differences among the 3 patches in adhesion. This small study was considered to be a pilot study, and the open study design with each subject receiving only the generic and placebo or the reference product instead of both test and reference applied simultaneously, does not provide any valid conclusions about differences in irritation with use of these products.

In this study, symptoms of opioid activity and withdrawal were exhibited by subjects in spite of premedication with Naltrexone, with more of the ADEs related to the active ingredient in the Duragesic arm than in the generic arm. The medical officer concluded that this difference in the occurrence of drug-related ADEs may be due to differences in drug absorption associated with observed differences in irritation potential.

A bioequivalence deficiency letter was sent to the sponsor on April 18, 2002 which stated in part "studies on assessing skin irritation and sensitization and patch adhesion are incomplete. You are requested to submit a new skin irritation/sensitization study using a parallel design and a sample size adequate to assess the potential for contact sensitization, for evaluation."

Current submission

The current submission, dated May 13, 2002, includes the sponsor's request for reconsideration of the need for further studies. The sponsor expresses concerns about the safety of exposing normal volunteers to the fentanyl, and indicates that the inactive components in the proposed product are widely used in topical and transdermal pharmaceutical products with already-known sensitization and irritation potentials.

The sponsor also presents two protocols for consideration in the event that the arguments against performing further studies are not accepted. Study FENT-0249 is an open-label, parallel, two-group single-period sensitization study in 400 healthy adult volunteers, randomized to receive either the Mylan fentanyl 25 μg/hr transdermal system or Duragesic® 25 μg/hr transdermal system. Patches are to be applied to different skin sites 3 times per week for a total of 9 patches followed by a 2 week rest period and then a 48 hour challenge application to a naïve site. Naltrexone is to be administered throughout the study, and opioid effects are to be monitored.

Study FENT-0252 is also an open-label, parallel, two-group single-period sensitization study in 400 healthy adult volunteers, randomized to receive either the Mylan fentanyl 25 μg/hr transdermal system and a placebo of the same system or Duragesic® 25 μg/hr transdermal system. Patches are to be applied to the exact same skin site 3 times per week for a total of 9 patches followed by a 2 week rest period and then a 48 hour challenge application to a naïve site. Naltrexone is to be administered throughout the study, and opioid effects are to be monitored.

A previous consultation from the Division of Anesthetic, Critical Care, and Addiction Drug Products (DACCADP) dated October 22, 2000 stated that the 25 μg/hr patch is too much fentanyl for an opioid naïve subject without pain, and would present a high risk of serious over sedation and respiratory depression. Further, using two patches (one generic and one reference product) for a total of 50 μg/hr would be dangerous in opioid naïve normal subjects. Two approaches were suggested to avoid the problems of opioid dependence and over-dosage. Normal subjects should be able to tolerate the use of the 50 μg/hr of fentanyl under continuous naltrexone blockade throughout the study period, with

careful attention to the period following final patch removal until serum fentanyl is completely cleared. The other approach would be to use opioid tolerant patients with chronic malignant or nonmalignant pain. However, the proposed dosing might not provide consistent pain control for these patients.

A current consultation from DACCADP regarding the results of FENT-0134 and the proposed protocols concluded that future studies utilizing repeated same-site application of the 25 μg/h dose or higher can not be considered safe to proceed. Review of data from study FENT-0134 revealed fentanyl levels of [redacted] from four subjects, three receiving Duragesic patches, and one receiving the Mylan patch. In contrast, the Duragesic product label describes fentanyl levels of 0.5 to 4.5 ng/ml following repeated doses of 100 μg/hr patch applied to different sites, and the mean fentanyl level following single 72-hour applications of the 25 μg/hr patch was 0.6 ng/ml with a standard deviation of 0.3.

Several options were provided for consideration in making future studies safer. The naltrexone dose could be increased in an attempt to further block the mu opioid receptors, but there is little data on how much additional protection would be offered by increasing the naltrexone dose or how much additional naltrexone would be sufficient. Other options include rotating the patch application sites or using a smaller patch size that delivers only 2.5 μg/hr, one tenth of the previously studies patch size, to allow a safety margin for blood levels of one order of magnitude. This sort of dose reduction is not possible for the reference Duragesic® patch due to the reservoir design.

A consultation from the Division of Dermatologic and Dental Drug Products (DDDDP) concluded that no valid conclusions could be drawn from FENT-0134 due to poor study design. A literature update on fentanyl hypersensitivity and skin reactions to fentanyl patches and a MedWatch update on cases of fentanyl causing contact dermatitis were suggested, and it was recommended that sponsors should be requested to do dermal safety testing with the placebo patch in sufficient numbers of patients to make a safety determination:

1. At least 30 evaluable subjects for cumulative patch irritation
2. At least 200 evaluable subjects for allergenicity/contact hypersensitivity

Discussion

The data submitted from Mylan's study FENT-0134 demonstrated that repeated same-site applications of the lowest approved dose of Duragesic® transdermal system, 25 μg/hr, may produce dangerously high serum fentanyl levels despite Naltrexone blockade. This may be due at least in part to increased absorption of fentanyl in skin that is irritated by the repeated same-site applications. (The approved Duragesic® label specifies that each new patch should be applied to a different skin site.) Because of this safety concern, the usual studies recommended in the *Guidance for Industry: Skin Irritation and Sensitization Testing of Generic Transdermal Drug Products* (December 1999) cannot be safely conducted. In fact, the reference product Duragesic® was approved without skin irritation and contact sensitization studies because of safety concerns with administering

narcotics in normal volunteers. (At the time that Duragesic® was approved, Naltrexone was not yet available, so there was no way to block the opioid effects for normal volunteers).

After careful consideration of this situation, in consultation with the Division of Anesthetic, Critical Care, and Addiction Drug Products (DACCADP) and the Division of Dermatologic and Dental Drug Products (DDDDP), it was decided that generic formulations of fentanyl transdermal systems should be evaluated for skin irritation and sensitization by testing a placebo patch that has all of the inactive ingredients and is identical in every manner except for the presence of fentanyl.

Such studies conducted with the placebo patches will not provide a direct comparison to the actual reference product and will not rule out the possibility that an increase in irritation may occur when the drug substance is added. However, some adhesive components are known to produce skin irritation, and given that the frequency and degree of skin reactions reported with the Duragesic® patches is relatively low, it is likely that these reactions are produced largely by the adhesive component.

An alternate approach might be comparative studies of skin reactions in patients randomized to take either the Mylan product or Duragesic® for the labeled indication and according to the labeled dosage and administration. While such a study would provide some comparative information regarding skin irritation with the use of the actual products, it would not provide the provocative same-site exposure that is usually required for dermal evaluation and would not evaluate the potential for sensitization.

Mylan Technologies, Inc. has presented results of studies that meet the necessary enrollment criteria and show that their transdermal system without the fentanyl does not produce as much irritation as the 0.1% or 0.2% sodium lauryl sulfite control (positive controls that produce mild irritation), and no cases of contact sensitization were observed.

The sponsor has also presented a literature overview of dermatological reactions produced by transdermal fentanyl, showing that such reactions are generally infrequent and mild. One study of 53 chronic cancer patients reported than $\geq$ 78% of patients on any assessment day showed no evidence of skin irritation at the patch site. Itching, edema, papules, and pustules were reported in 2-8% of the patients during the study. The sponsor reports that from the period of March 1983 through December 2000 (over 17 years) a total of 1,583 skin sensitization and irritation adverse events associated with fentanyl administration were reported to the FDA, including administration by transdermal, topical, or intradermal routes, as well as reports in which no route or dosage is listed. This is the best available information to suggest that the degree of irritation and sensitization seen with use of the Mylan placebo patch in the studies presented is no more than that expected with the approved reference product.

FENT-0132 and –0133 both included adhesion assessments at each visit using the following scoring system:

0	90% adherence	Essentially no lift off of the skin
1	75-89% adherence	Some edges only lifting off of the skin
2	50-74% adherence	Less than half of the TDS lifting off of the skin
3	<50% adherence	Not detached, but more than half of the TDS lifting off of the skin
4	0% adherence	Detached; patch completely off of the skin

The mean adhesion score for the TDS placebo in FENT-0123 was 0.14. Of 219 subjects with at least 1 adhesion assessment, 215 subjects (98%) had a mean adhesion score of <1.0 for the placebo system, and 165 subjects (75%) had a mean adhesion score of 0. A total of 33 subjects (15%) had at least one placebo patch that detached completely (score of 4). Only four subjects had a mean score >1. Three of these were between 1 and 2, and the other one was over 3.

In FENT-0133 the mean adhesion score for the TDS placebo was 0.29, and only 3 subjects had a score of 1 or greater. One subject was discontinued after a single application that resulted in complete detachment of the TDS placebo.
These results confirm an acceptable degree of patch adhesion for a transdermal delivery system.

Recommendations to the sponsor

Your proposed protocols FENT-0249 and FENT-0252 are not acceptable. FENT-0252 cannot be considered sufficiently safe to proceed, and the rotating patch design in FENT-0249 is inadequate as a provocative irritation and sensitization study.

No further studies of dermal irritation and sensitization or patch adhesion are required for your proposed fentanyl transdermal system. The data from FENT-0134 demonstrate that repeated same-site applications of the 25 µg/hr dose can result in dangerously high serum fentanyl concentrations, making it unsafe to conduct the provocative studies that would otherwise be needed. The small number of subjects and open design with between-subject comparison do not provide any meaningful comparison of dermal reactions between the Mylan product and Duragesic®. However, studies FENT-0132 and FENT-0133, along with your literature overview of dermatological reactions produced by transdermal fentanyl, are adequate to demonstrate that use of your Fentanyl Transdermal System is unlikely to result in a degree of skin irritation or sensitization that is greater than that seen with use of the reference product Duragesic® Transdermal System.

Dena R. Hixon MD 9/18/02

Dena R. Hixon, M.D.
Associate Director for Medical Affairs
Office of Generic Drugs

ANDA 76-258

Drug Product:	**Fentanyl Transdermal System 25 μg/hr**
Sponsor:	**Mylan Technologies, Inc.**
Reference Listed Drug:	**Duragesic Transdermal System, Janssen Pharmaceuticals**
Date of review:	**September 19, 2002**
Reviewer:	**Dena R. Hixon, M.D.** **Associate Director for Medical Affairs**

The bioequivalency deficiency letter sent to Mylan on April 16, 2002 includes the following as deficiency #4:

"Study FENT-0134 contains some pharmacokinetic data. In order to evaluate those data, you are requested to calculate appropriate pharmacokinetic parameters and statistically compare PK parameters of the test and RLD."

This comment was addressed in the bioequivalency review. Since the objective of the study was to evaluate skin irritation and sensitization by repetitive applications to the same skin site, plasma concentrations were periodically determined to assess the effect of repeated same-site patch applications, not for bioequivalence purposes. Therefore, a comparison of these parameters of the test and RLD would not provide additional useful information, and should not be requested.

Recommendation to sponsor:
After further review of FENT-0134, you are no longer requested to provide further information about pharmacokinetic data from that study.

Dena R. Hixon MD

Dena R. Hixon, M.D.
Associate Director for Medical Affairs
Office of Generic Drugs

APPEARS THIS WAY
ON ORIGINAL

Recommendations for Skin Irritation and Sensitization Studies for Generic Fentanyl Transdermal Systems

Reference Listed Drug: Duragesic® Transdermal System, Janssen Pharmaceuticals

The *Guidance for Industry: Skin Irritation and Sensitization Testing of Generic Transdermal Drug Products* (December 1999) recommends skin irritation and sensitization studies with repeated same-site applications of both the generic and reference products to the same subjects three times weekly for a total of 9 sequential applications. Such repeated applications of the lowest approved dose of a fentanyl transdermal system, 25 μg/hr, have been shown to produce dangerously high serum fentanyl levels, even when subjects are randomized to receive only one patch and are treated with Naltrexone blockade throughout the study.

Because this serious safety concern precludes the usual comparative studies, the Office of Generic Drugs (OGD), in consultation with the Division of Anesthetic, Critical Care, and Addiction Drug Products (DACCADP) and the Division of Dermatologic and Dental Drug Products (DDDDP), recommends that generic fentanyl transdermal systems should be evaluated for skin irritation and sensitization by testing a placebo patch that has all of the inactive ingredients and is identical to the sponsor's proposed product in every manner except for the absence of fentanyl.

The study design should be similar to that described in the *Guidance for Industry: Skin Irritation and Sensitization Testing of Generic Transdermal Drug Products* (December 1999), using the placebo patch and positive and negative controls for irritation potential. At least 30 evaluable subjects are needed for cumulative patch irritation testing, and at least 200 evaluable subjects are needed for allergenicity/contact hypersensitivity testing. These studies can be combined into a single study as discussed in the above-mentioned Guidance.

The study results should show that the proposed product is no more irritating than a positive control that produces mild irritation. The sponsor should also present a literature update on fentanyl hypersensitivity and skin reactions to fentanyl patches and any additional information they may have regarding controlled studies of fentanyl-induced irritation or contact sensitization to support that the proposed product is not likely to produce any greater degree of irritation or sensitization than that observed with use of the reference product.

The Office of Generic Drugs recommends that protocols be submitted for review and comment prior to conducting the studies.

Dena R. Hixon MD 9/19/02

Dena R. Hixon, M.D.
Associate Director for Medical Affairs
Office of Generic Drug
September 18, 2002

John P. Leonard 9/19/02

Attachment: Medical Reviews

ANDA 76-258

Drug Product:	**Fentanyl Transdermal System 25 μg/hr**
Sponsor:	**Mylan Technologies, Inc.**
Reference Listed Drug:	**Duragesic Transdermal System, Janssen Pharmaceuticals**
Date of review:	**September 19, 2002**
Reviewer:	**Dena R. Hixon, M.D.**

Associate Director for Medical Affairs

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This comment was addressed in the bioequivalency review. Since the objective of the study was to evaluate skin irritation and sensitization by repetitive applications to the same skin site, plasma concentrations were periodically determined to assess the effect of repeated same-site patch applications, not for bioequivalence purposes. Therefore, a comparison of these parameters of the test and RLD would not provide additional useful information, and should not be requested.

Recommendation to sponsor:
After further review of FENT-0134, you are no longer requested to provide further information about pharmacokinetic data from that study.

Dena R. Hixon, M.D.
Associate Director for Medical Affairs
Office of Generic Drugs

APPEARS THIS WAY
ON ORIGINAL

ANDA 76-258

CD 02-369
P 02-026

Drug Product:	**Fentanyl Transdermal System 25 μg/hr**
Sponsor:	**Mylan Technologies, Inc.**
Reference Listed Drug:	**Duragesic Transdermal System, Janssen Pharmaceuticals**
Date of submission:	**May 13, 2002**
Date of CD:	**June 21, 2002**
Date of review:	**September 18, 2002**
Reviewer:	**Dena R. Hixon, M.D.** **Associate Director for Medical Affairs**

Background

Fentanyl Transdermal System provides continuous systemic delivery of fentanyl, a potent opioid analgesic, for 72 hours. It is indicated for the management of chronic pain that cannot be managed by lesser means.

Mylan Technologies, Inc. submitted ANDA 76-258 for Fentanyl Transdermal System on October 12, 2001. The Mylan system differs from the reference product in that the delivery system for the reference product includes a drug reservoir with a membrane that controls the rate of delivery of fentanyl to the skin surface, while the Mylan product contains a fentanyl-silicone adhesive matrix layer. A bioequivalence review found the in-vivo bioequivalence study acceptable.

The application included five studies assessing skin irritation and sensitization. Two of these studies were animal studies and were not reviewed by the medical officer. The following three human studies were reviewed and found to be inadequate to compare the generic product to the reference product.

1. FENT-0132 "A Randomized, Controlled Study to Evaluate the Sensitizing Potential of a Transdermal Delivery System for Fentanyl in Healthy Volunteers, Using a Human Repeat Insult Patch Test Design" was a randomized controlled within-subject comparison to evaluate the potential for induction of contact sensitization and irritation with use of Mylan's system compared to a positive and negative control. The study enrolled 230 subjects, of which 202 were included in the final analysis. Each subject received a placebo patch (identical to the fentanyl transdermal system except for the absence of fentanyl), a positive control patch of sodium lauryl sulfate (SLS) 0.1% aqueous solution applied under occlusive patch conditions, and an open unpatched area as a negative control. The patches were applied to the same skin site three times per week for a total of 9 consecutive applications, and skin irritation was evaluated with a standard scoring system at each patch change. After a 2-week patch-free interval, a 48-hour application of each system to a naïve site was used to test for reactions indicative of contact sensitization.

   The fentanyl placebo patch was found to be less irritating that the SLS, and the SLS led to

sufficient irritation to require patch removal much more frequently and much earlier in the study than did the generic placebo. No contact sensitization reactions were noted. The reviewer concluded that the observations in this study on skin irritation and contact sensitization potential cannot be extrapolated to the fentanyl generic transdermal system because the active ingredient is contained within the adhesive of the generic transdermal system.

2. FENT-0133: "A 21-day, Randomized, Controlled Study to Evaluate the Local Tolerability of a Transdermal Delivery System for Fentanyl in Healthy Volunteers, Using a Cumulative Irritant Patch Test Design" was a randomized controlled within-subject comparative study of the test and positive and negative controls under occlusive conditions. The study enrolled 41 subjects, and 35 subjects were included in the analysis. They each received a fentanyl transdermal system placebo, a positive control of sodium lauryl sulfate (SLS) 0.2% aqueous solution, and a negative control of saline, 0.9%. Mean and cumulative total irritation scores were calculated using a standard scoring system.

   The placebo patch was less irritating than the SLS control and was comparable to the saline control for mean irritation score. The SLS produced significant and early irritation, and 33 of the SLS patches had to be discontinued due to grade 3 irritation. The reviewer concluded that this study does not provide comparative information on the skin irritation potential of the generic product compared to its reference listed drug.

3. FENT-0134: "Evaluation of contact sensitization potential of Fentanyl Transdermal System in Normal Healthy Volunteers" was an open-label parallel, two-group controlled study in which 42 subjects (28 evaluable) were randomized to receive either one Fentanyl Transdermal System 25 μg/hr and one placebo transdermal system or one Duragesic® Transdermal System 25 μg/hr and an alternative open (unpatched) site. Patches were applied 3 times a week for 48 to 72 hours, for a total of 9 consecutive applications to the same site. Naltrexone 50 mg twice a day was started 24 hours prior to the first test system application and continued through the induction phase. Scoring for irritation was performed at each patch change. Following a two-week rest, another patch was applied to a naïve site for 48 hours (along with Naltrexone 100 mg/day for 4 days) to test for sensitization reactions.

   The Fentanyl generic was the least irritating of the 3 patches, and the Duragesic® patch was the most irritating. There were no sensitization reactions. The sponsor's adhesion analysis showed no significant differences among the 3 patches in adhesion.
   This small study was considered to be a pilot study, and the open study design with each subject receiving only the generic and placebo or the reference product instead of both test and reference applied simultaneously, does not provide any valid conclusions about differences in irritation with use of these products.

   In this study, symptoms of opioid activity and withdrawal were exhibited by subjects in spite of premedication with Naltrexone, with more of the ADEs related to the active ingredient in the Duragesic arm than in the generic arm. The medical officer concluded that this difference in the occurrence of drug-related ADEs may be due to differences in drug absorption associated with observed differences in irritation potential.

A bioequivalence deficiency letter was sent to the sponsor on April 18, 2002 which stated in part "studies on assessing skin irritation and sensitization and patch adhesion are incomplete. You are requested to submit a new skin irritation/sensitization study using a parallel design and a sample size adequate to assess the potential for contact sensitization, for evaluation."

Current submission

The current submission, dated May 13, 2002, includes the sponsor's request for reconsideration of the need for further studies. The sponsor expresses concerns about the safety of exposing normal volunteers to the fentanyl, and indicates that the inactive components in the proposed product are widely used in topical and transdermal pharmaceutical products with already-known sensitization and irritation potentials.

The sponsor also presents two protocols for consideration in the event that the arguments against performing further studies are not accepted. Study FENT-0249 is an open-label, parallel, two-group single-period sensitization study in 400 healthy adult volunteers, randomized to receive either the Mylan fentanyl 25 μg/hr transdermal system or Duragesic® 25 μg/hr transdermal system. Patches are to be applied to different skin sites 3 times per week for a total of 9 patches followed by a 2 week rest period and then a 48 hour challenge application to a naïve site. Naltrexone is to be administered throughout the study, and opioid effects are to be monitored.

Study FENT-0252 is also an open-label, parallel, two-group single-period sensitization study in 400 healthy adult volunteers, randomized to receive either the Mylan fentanyl 25 μg/hr transdermal system and a placebo of the same system or Duragesic® 25 μg/hr transdermal system. Patches are to be applied to the exact same skin site 3 times per week for a total of 9 patches followed by a 2 week rest period and then a 48 hour challenge application to a naïve site. Naltrexone is to be administered throughout the study, and opioid effects are to be monitored.

A previous consultation from the Division of Anesthetic, Critical Care, and Addiction Drug Products (DACCADP) dated October 22, 2000 stated that the 25 μg/hr patch is too much fentanyl for an opioid naïve subject without pain, and would present a high risk of serious over sedation and respiratory depression. Further, using two patches (one generic and one reference product) for a total of 50 μg/hr would be dangerous in opioid naïve normal subjects. Two approaches were suggested to avoid the problems of opioid dependence and over-dosage. Normal subjects should be able to tolerate the use of the 50 μg/hr of fentanyl under continuous naltrexone blockade throughout the study period, with careful attention to the period following final patch removal until serum fentanyl is completely cleared. The other approach would be to use opioid tolerant patients with chronic malignant or nonmalignant pain. However, the proposed dosing might not provide consistent pain control for these patients.

A current consultation from DACCADP regarding the results of FENT-0134 and the proposed protocols concluded that future studies utilizing repeated same-site application of the 25 μg/h dose or higher can not be considered safe to proceed. Review of data from study FENT-0134 revealed fentanyl levels of [redacted] from four subjects, three receiving Duragesic patches, and one receiving the Mylan patch. In contrast, the Duragesic product label describes

fentanyl levels of 0.5 to 4.5 ng/ml following repeated doses of 100 μg/hr patch applied to different sites, and the mean fentanyl level following single 72-hour applications of the 25 μg/hr patch was 0.6 ng/ml with a standard deviation of 0.3.

Several options were provided for consideration in making future studies safer. The naltrexone dose could be increased in an attempt to further block the mu opioid receptors, but there is little data on how much additional protection would be offered by increasing the naltrexone dose or how much additional naltrexone would be sufficient. Other options include rotating the patch application sites or using a smaller patch size that delivers only 2.5 μg/hr, one tenth of the previously studies patch size, to allow a safety margin for blood levels of one order of magnitude. This sort of dose reduction is not possible for the reference Duragesic® patch due to the reservoir design.

A consultation from the Division of Dermatologic and Dental Drug Products (DDDDP) concluded that no valid conclusions could be drawn from FENT-0134 due to poor study design. A literature update on fentanyl hypersensitivity and skin reactions to fentanyl patches and a MedWatch update on cases of fentanyl causing contact dermatitis were suggested, and it was recommended that sponsors should be requested to do dermal safety testing with the placebo patch in sufficient numbers of patients to make a safety determination:

1. At least 30 evaluable subjects for cumulative patch irritation
2. At least 200 evaluable subjects for allergenicity/contact hypersensitivity

scussion

The data submitted from Mylan's study FENT-0134 demonstrated that repeated same-site applications of the lowest approved dose of Duragesic® transdermal system, 25 μg/hr, may produce dangerously high serum fentanyl levels despite Naltrexone blockade. This may be due at least in part to increased absorption of fentanyl in skin that is irritated by the repeated same-site applications. (The approved Duragesic® label specifies that each new patch should be applied to a different skin site.) Because of this safety concern, the usual studies recommended in the *Guidance for Industry: Skin Irritation and Sensitization Testing of Generic Transdermal Drug Products* (December 1999) cannot be safely conducted. In fact, the reference product Duragesic® was approved without skin irritation and contact sensitization studies because of safety concerns with administering narcotics in normal volunteers. (At the time that Duragesic® was approved, Naltrexone was not yet available, so there was no way to block the opioid effects for normal volunteers).

After careful consideration of this situation, in consultation with the Division of Anesthetic, Critical Care, and Addiction Drug Products (DACCADP) and the Division of Dermatologic and Dental Drug Products (DDDDP), it was decided that generic formulations of fentanyl transdermal systems should be evaluated for skin irritation and sensitization by testing a placebo patch that has all of the inactive ingredients and is identical in every manner except for the presence of fentanyl.

Such studies conducted with the placebo patches will not provide a direct comparison to the actual reference product and will not rule out the possibility that an increase in irritation may

occur when the drug substance is added. However, some adhesive components are known to produce skin irritation, and given that the frequency and degree of skin reactions reported with the Duragesic® patches is relatively low, it is likely that these reactions are produced largely by the adhesive component.

An alternate approach might be comparative studies of skin reactions in patients randomized to take either the Mylan product or Duragesic® for the labeled indication and according to the labeled dosage and administration. While such a study would provide some comparative information regarding skin irritation with the use of the actual products, it would not provide the provocative same-site exposure that is usually required for dermal evaluation and would not evaluate the potential for sensitization.

Mylan Technologies, Inc. has presented results of studies that meet the necessary enrollment criteria and show that their transdermal system without the fentanyl does not produce as much irritation as the 0.1% or 0.2% sodium lauryl sulfite control (positive controls that produce mild irritation), and no cases of contact sensitization were observed.

The sponsor has also presented a literature overview of dermatological reactions produced by transdermal fentanyl, showing that such reactions are generally infrequent and mild. One study of 53 chronic cancer patients reported than $\geq$ 78% of patients on any assessment day showed no evidence of skin irritation at the patch site. Itching, edema, papules, and pustules were reported in 2-8% of the patients during the study. The sponsor reports that from the period of March 1983 through December 2000 (over 17 years) a total of 1,583 skin sensitization and irritation adverse events associated with fentanyl administration were reported to the FDA, including administration by transdermal, topical, or intradermal routes, as well as reports in which no route or dosage is listed. This is the best available information to suggest that the degree of irritation and sensitization seen with use of the Mylan placebo patch in the studies presented is no more than that expected with the approved reference product.

FENT-0132 and –0133 both included adhesion assessments at each visit using the following scoring system:

0	90% adherence	Essentially no lift off of the skin
1	75-89% adherence	Some edges only lifting off of the skin
2	50-74% adherence	Less than half of the TDS lifting off of the skin
3	<50% adherence	Not detached, but more than half of the TDS lifting off of the skin
4	0% adherence	Detached; patch completely off of the skin

The mean adhesion score for the TDS placebo in FENT-0123 was 0.14. Of 219 subjects with at least 1 adhesion assessment, 215 subjects (98%) had a mean adhesion score of <1.0 for the placebo system, and 165 subjects (75%) had a mean adhesion score of 0. A total of 33 subjects (15%) had at least one placebo patch that detached completely (score of 4). Only four subjects had a mean score >1. Three of these were between 1 and 2, and the other one was over 3.

In FENT-0133 the mean adhesion score for the TDS placebo was 0.29, and only 3 subjects had a

score of 1 or greater. One subject was discontinued after a single application that resulted in complete detachment of the TDS placebo.
These results confirm an acceptable degree of patch adhesion for a transdermal delivery system.

Recommendations to the sponsor

Your proposed protocols FENT-0249 and FENT-0252 are not acceptable. FENT-0252 cannot be considered sufficiently safe to proceed, and the rotating patch design in FENT-0249 is inadequate as a provocative irritation and sensitization study.

No further studies of dermal irritation and sensitization or patch adhesion are required for your proposed fentanyl transdermal system. The data from FENT-0134 demonstrate that repeated same-site applications of the 25 μg/hr dose can result in dangerously high serum fentanyl concentrations, making it unsafe to conduct the provocative studies that would otherwise be needed. The small number of subjects and open design with between-subject comparison do not provide any meaningful comparison of dermal reactions between the Mylan product and Duragesic®. However, studies FENT-0132 and FENT-0133, along with your literature overview of dermatological reactions produced by transdermal fentanyl, are adequate to demonstrate that use of your Fentanyl Transdermal System is unlikely to result in a degree of skin irritation or sensitization that is greater than that seen with use of the reference product Duragesic® Transdermal System.

Dena R. Hixon, M.D.
Associate Director for Medical Affairs
Office of Generic Drugs

NOV 22 2002

BIOEQUIVALENCY DEFICIENCIES

ANDA/AADA: 76-258 APPLICANT: Mylan Technologies, Inc.

DRUG PRODUCT: FENTANYL TRANSDERMAL PATCH 25, 50, 75 and 100 mcg/hr

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiencies have been identified:

1. Your proposed protocols FENT-0249 and FENT-0252 are not acceptable. FENT-0252 cannot be considered sufficiently safe to proceed, and the rotating patch design in FENT-0249 is inadequate as a provocative irritation and sensitization study. No further studies of dermal irritation and sensitization or patch adhesion are required for your proposed fentanyl transdermal system.

   The data from FENT-0134 demonstrate that repeated same-site applications of the 25 µg/hr dose can result in dangerously high serum fentanyl concentrations, making it unsafe to conduct the provocative studies that would otherwise be needed. The small number of subjects and open design with between-subject comparison do not provide any meaningful comparison of dermal reactions between the Mylan product and Duragesic®. However, studies FENT-0132 and FENT-0133, along with your literature overview of dermatological reactions produced by transdermal fentanyl, are adequate to demonstrate that use of your Fentanyl Transdermal System is unlikely to result in a degree of skin irritation or sensitization that is greater than that seen with use of the reference product Duragesic® Transdermal System.

2. After further review of FENT-0134, you are no longer requested to provide further information about pharmacokinetic data from that study.

APPEARS THIS WAY
ON ORIGINAL

3. The dissolution testing data is incomplete. You are requested to conduct comparative dissolution testing on 12 individual dosage units for the test and reference products. Dissolution testing should be conducted in different media _____ using discriminating agitation speed and multipoint dissolution profiles should be obtained. Adequate sampling times should be performed (See current USP Section <711> and <724> for general dissolution requirements).

Sincerely yours,

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

NOV 20 2002

Fentanyl Transdermal System
25, 50, 75 and 100 mcg/h
ANDA 76-258
Reviewer: Nhan L. Tran
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Mylan Technologies
St. Albans, VT 05478
Submission date:
December 4, 2001

Review of a Waiver Request

BACKGROUND

On October 12, 2001, Mylan Technologies submitted results of a clinical and a biostudy on the 25 mcg/hr strength. The submission was reviewed and found incomplete, in the areas of clinical and dissolution studies. The deficiency letter was sent to the firm on April 18, 2002.

Subsequently, Mylan Technologies submitted an amendment on May 13, 2002 to respond to the clinical deficiency. In the submission, the Sponsor argued for not conducting additional studies because of the Sponsor's concern about the safety of exposing normal volunteers to the fentanyl and the inactive components of the proposed product are widely used in topical and transdermal products with known sensitization and skin irritation potentials.

The firm also submitted two protocols (FENT-0249 and FENT-0252) for review in the event that the firm's request for not conducting additional clinical studies was not accepted. The Medical Officer has reviewed the two protocols and the review is attached at the end of this document, for information.

After reviewing the protocols, the Medical Officer has made the following recommendations:

Protocols FENT-0249 and FENT-0252 are not acceptable because:

- Protocol FENT-0249 is inadequate as a provocative irritation and sensitization study.
- Protocol FENT-0252 cannot be considered sufficiently safe to proceed
- No further studies of dermal irritation and sensitization or patch adhesion are required for the Sponsor's transdermal system.

Also in the submission dated October 12, 2001, the firm stated that the clinical study (FENT-0134) contained some pharmacokinetic data but the data was not included in the submission. The DBE has requested in a deficiency letter to Mylan to calculate appropriate pharmacokinetic parameters and to statistically compare PK parameters of the test and RLD. On September 18, 2002, after further review of the clinical study FENT-0134, the Medical Officer has recommended that the firm is no longer requested to provide further information about pharmacokinetic data from that study. The DBE concurred with the recommendation.

REVIEW OF THE WAIVER REQUEST:

Mylan Technologies states that its Fentanyl Transdermal System, 25 mcg/hr, 50 mcg/hr, 75 mcg/hr and 100 mcg/hr are compositionally proportional. The Sponsor affirms that the only difference between systems is area. The 25 mcg/hr system has a 6.25 cm^2 active area, the 50 mcg/hr system has a 12.5 cm^2 active area, the 75 mcg/hr system has a 18.75 cm^2 active area, and the 100 mcg/hr system has a 25 cm^2 active area. Based on 21 CFR 320.22(d)(2) and based on the results of the BE study conducted on 25 mcg/hr strength, dissolution data and formulation information, the firm is requesting a waiver for its transdermal products, 50 mcg/hr, 75 mcg/hr and 100 mcg/hr strengths.

PRODUCT FORMULATION:

The firm provided the following formulation information on all strengths:

QUANTITATIVE COMPOSITION:

Composition	Theoretical (Quantity/Patch)			
	25 mcg/hr	50 mcg/hr	75 mcg/hr	100 mcg/hr
ACTIVE				
Fentanyl	2.55 mg	5.10 mg	7.65 mg	10.20 mg
INACTIVE				
Silicone Adhesive				
Dimethicone NF				
Component Total				
BACKING				
Polyolefin Film	6.25 cm^2	12.5 cm^2	18.75 cm^2	25 cm^2

It is noted the formulations for Mylan's Fentanyl Transdermal Systems, 50 mcg/hr, 75 mcg/hr and 100 mcg/hr, are proportionally similar to the 25 mcg/hr strength. In addition the patches are constructed from the same transdermal extended release film and differ only in the patch size. The composition per unit area of all system sizes is identical. The amount of fentanyl released from each system per hour is proportional to the surface area. The transdermal system is supposed to provide continuous 72 hour systemic delivery of fentanyl.

COMPARATIVE IN-VITRO DISSOLUTION TESTING RESULTS:

The firm submitted the following dissolution information. The firm used the USP . The apparatus has been used for this type of dosage form.

Strengths	25 MCG/HR		50 MCG/HR		75 MCG/HR		100 MCG/HR	
Lot #	R6J0001	9910472	R6J0011	0109258	R6J0010	0108818	R6J0008	9910192
Time (hour)	(Test)	(Ref)	(Test)	(Ref)	(Test)	(Ref)	(Test)	(Ref)
0.5 hr								
MEAN	**29**	**15**	**28**	**10**	**28**	**9**	**28**	**10**
CV%	3.6	5.2	2.1	4	5.2	4.9	2.2	6.4
MIN								
MAX								
1 hr								
MEAN	**44**	**18**	**43**	**12**	**43**	**12**	**45**	**13**
CV%	3	3.7	2.5	2	4	4.8	1.7	6.5
MIN								
MAX								
2 hrs								
MEAN	**64**	**23**	**62**	**15**	**63**	**14**	**63**	**15**
CV%	3.4	2.3	1.4	3.5	2.8	4.4	1	6.4
MIN								
MAX								
4 hrs								
MEAN	**85**	**29**	**82**	**19**	**84**	**19**	**82**	**19**
CV%	2.5	2.8	1.3	3.4	2	4.4	1.4	6.5
MIN								
MAX								
8 hrs								
MEAN	**97**	**39**	**93**	**28**	**96**	**26**	**92**	**26**
CV%	2	3.4	0.6	3.8	1.6	5.4	1.6	6.8
MIN								
MAX								
24 hrs								
MEAN	**102**	**60**	**97**	**50**	**102**	**45**	**94**	**45**
CV%	2.1	4.9	1.2	4.5	1.2	7.7	1.3	6.3
MIN								
MAX								

DEFICIENCIES:

1. The dissolution testing conducted by the firm is incomplete. The firm is requested to conduct comparative dissolution testing on all strengths for the test and reference products. Dissolution testing should be conducted on 12 individual dosage units, in different media ( ) and multipoint dissolution profiles should be obtained.

RECOMMENDATION:

This submission submitted by Mylan is incomplete per Deficiencies above. The firm should be informed of the Deficiency.

Nhan L. Tran, Ph.D.
Review Branch II

RD INITIALLED SNERURKAR
FT INITIALLED SNERURKAR 8/29/2002

Concur: Date: 11/20/02
Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence

CC: ANDA 76-258 (original), HFD 655 (Tran, Nerurkar), Drug File, Division File

APPEARS THIS WAY
ON ORIGINAL

BIOEQUIVALENCY DEFICIENCIES

ANDA/AADA: 76-258 APPLICANT: Mylan Technologies, Inc.

DRUG PRODUCT: FENTANYL TRANSDERMAL PATCH 25, 50, 75 and 100 mcg/hr

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiencies have been identified:

1. Your proposed protocols FENT-0249 and FENT-0252 are not acceptable. FENT-0252 cannot be considered sufficiently safe to proceed, and the rotating patch design in FENT-0249 is inadequate as a provocative irritation and sensitization study. No further studies of dermal irritation and sensitization or patch adhesion are required for your proposed fentanyl transdermal system.

   The data from FENT-0134 demonstrate that repeated same-site applications of the 25 µg/hr dose can result in dangerously high serum fentanyl concentrations, making it unsafe to conduct the provocative studies that would otherwise be needed. The small number of subjects and open design with between-subject comparison do not provide any meaningful comparison of dermal reactions between the Mylan product and Duragesic®. However, studies FENT-0132 and FENT-0133, along with your literature overview of dermatological reactions produced by transdermal fentanyl, are adequate to demonstrate that use of your Fentanyl Transdermal System is unlikely to result in a degree of skin irritation or sensitization that is greater than that seen with use of the reference product Duragesic® Transdermal System.

2. After further review of FENT-0134, you are no longer requested to provide further information about pharmacokinetic data from that study.

3. The dissolution testing data is incomplete. You are requested to conduct comparative dissolution testing on 12 individual dosage units for the test and reference products. Dissolution testing should be conducted in different media using discriminating agitation speed and multipoint dissolution profiles should be obtained. Adequate sampling times should be performed (See current USP Section <711> and <724> for general dissolution requirements).

Sincerely yours,

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

CC: ANDA
ANDA DUPLICATE
DIVISION FILE
FIELD COPY
DRUG FILE

Endorsements: (Draft and Final with Dates)
HFD-655/Reviewer 10/17
HFD-655/Bio Team Leader 10/29/02 10/21/02
HFD-617/Project Manager
HFD-650/Dale Conner 11/20/02

BIOEQUIVALENCY – DEFICIENCIES

Submission Date:
December 4, 2001

1. **DISSOLUTION DATA** (DIS)

Strengths: 50 mcg/hr
Outcome: IC

2. **DISSOLUTION DATA** (DIS)

Strengths: 75 mcg/hr
Outcome: IC

3. **DISSOLUTION DATA** (DIS)

Strengths: 100 mcg/hr
Outcome: IC

Outcome Decisions:

IC - Incomplete

WinBio Comments

APPEARS THIS WAY
ON ORIGINAL

APR 18 2002

BIOEQUIVALENCY DEFICIENCIES

ANDA/AADA: 76-258 APPLICANT: Mylan Technologies, Inc.

DRUG PRODUCT: FENTANYL TRANSDERMAL PATCH 25 mcg/hr

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiencies have been identified:

1. You have conducted 3 studies and none of them represent an ideal design to test for skin irritation and sensitization potential of the generic transdermal compared to its reference listed product.

In the first study (FENT-0132) comparing the fentanyl placebo patch with a positive control (SLS) and a negative control, the placebo patch was found to be significant less irritating the SLS patch. There were no contact sensitization reactions noted in this study. The study did not include either the test or reference products. Since the active ingredient is contained within the adhesive of the generic transdermal, the placebo patch without fentanyl is not comparable to the patch with the active ingredient. Therefore, the observations in this study on skin irritation and contact sensitization potential cannot be extrapolated to Mylan's transdermal system.

In the second study (FENT-0133) comparing the irritation potential of the fentanyl generic transdermal to that of two controls, the fentanyl system is comparable to the saline control, but this study does not provide information on the skin irritation potential of the generic product comparable to its reference listed drug.

The third study (FENT-0134) compared the fentanyl generic transdermal system to the placebo transdermal system in 14 subjects and the Duragesic transdermal system to an open unpatched site in another 15 subjects. The fentanyl generic was the least irritating of the three patches, and the generic placebo was a bit more irritating than the same patch with active fentanyl. The Duragesic patch was the most irritating of the three, and the fentanyl generic was significantly less irritating. However, the generic patch without the active drug product in its adhesive matrix had a mean irritation

score that approached that of the Duragesic patch. The fentanyl generic was not significantly different from its placebo. There were no sensitization reactions in this study. This study appears to be a pilot study with a very small sample size. These preliminary data suggest that Mylan's fentanyl transdermal system is less irritating than the Duragesic transdermal system and leads to fewer ADEs associated with the active product. Therefore, this observation suggests that the generic product is not equivalent from at least a safety point of view when chronically administered.

In addition, you conducted two studies, one on irritation and a second on sensitization in animals. However, the recommended studies are to be conducted in humans. The required testing is outlined in the guidance: *Guidance for Industry: Skin Irritation and Sensitization Testing of Generic Transdermal Drug Products, December 1999.*

You did not conduct the studies that are recommended in the guidance. Due, possibly, to concern over exposing normal volunteers to a potentially habituating drug (fentanyl), you have used naltraxone blockade of the fentanyl effect. You appeared to have been reluctant to use the traditional design of applying 2 patches with active drug at the same time in a single patient. Therefore, instead of simultaneously testing the generic and reference listed drug in the same individual, you have chosen to conduct a small parallel group study comparing the two. Despite the small number of patients and because the Duragesic® patch is somewhat irritating, you have been able to demonstrate that the generic patch is less irritating than the reference listed drug and that neither cause sensitization. The study is too small to make any conclusions on the contact sensitization potential and the observed differences in skin irritation have not been analyzed by the FDA statistician.
Hence, studies on assessing skin irritation and sensitization and patch adhesion are incomplete. You are requested to submit a new skin irritation/sensitization study using a parallel design and a sample size adequate to assess the potential for contact sensitization, for evaluation. Please refer to the Agency's guidance: *Guidance for Industry: Skin Irritation and Sensitization Testing of Generic Transdermal Drug Products, December 1999* for more information. This guidance is available on the internet at: http://www.fda.gov/cder/guidance/index.htm

2. The dissolution testing data is incomplete. You are requested to conduct dissolution testing on 12 individual dosage units for the test and reference products. Dissolution testing should be conducted in different media [redacted] and multipoint dissolution profiles should be obtained using discriminating agitation speed. A surfactant may be used with appropriate justification. Adequate sampling times should be performed (See current USP Sections <711> and <724> for general dissolution requirements).

3. Please indicate how [redacted] was prepared. The USP indicates that pH of the [redacted] cannot go below [redacted] See USP 24 page 2232).

4. Study FENT-0134 contains some pharmacokinetic data. In order to evaluate those data, you are requested to calculate appropriate pharmacokinetic parameters and statistically compare PK parameters of the test and RLD.

5. Please submit all analytical SOPs including the one for sample repeats.

Sincerely yours,

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

Fentanyl Transdermal System
25 µg/h
ANDA 76-258
Reviewer: Nhan L. Tran
V:\firmsam\mylan\ltrs&rev\76258N0701.doc

Mylan Technologies
St. Albans, VT 05478
Submission date:
October 12, 2001

Review of an In-Vivo Bioequivalence Study

(An Electronic Submission)

BACKGROUND

Fentanyl is an opioid analgesic that interacts predominately with the opioid μ-receptor. These μ-binding sites are discretely distributed in the human brain, spinal cord, and other tissues. Fentanyl exerts its principal pharmacologic effects on the central nervous system and its primary actions of therapeutic value are analgesia and sedation. The most common adverse reactions reported for fentanyl were nausea, vomiting, constipation, dry mouth, somnolence, confusion and sweating. Hypoventilation was the most serious adverse reaction observed with the use of fentanyl. Significant amounts of fentanyl are absorbed from the skin for 17 hours or more after the system is removed.

Following the initial application of fentanyl, serum fentanyl concentrations increase gradually, generally leveling off between 12 and 24 hours and remaining relatively constant, with some fluctuation, for the remainder of the 72 hours. After initial application, peak serum levels of fentanyl generally occurred between 24 and 72 hours. Serum fentanyl concentrations decline gradually, falling about 50% in approximately 17 hours after the system removal.
Initial recommended dose is 25 μg/h in most patients.

The RLD is Duragesic® by Janssen Pharmaceuticals, available in four (4) strengths: 25, 50, 75 and 100 μg/h. Duragesic® is a transdermal system providing continuous 72 hour systemic delivery of fentanyl. The amount of fentanyl released from each system per hour is proportional to the surface area. The composition per unit area of all system sizes is identical.

HISTORICAL INFORMATION

There is no generic version of Duragesic® at the present time. The Orange Book (OB) lists only the RLD. No BE studies were found in the Division Drug Files. Several protocols and Control Documents were submitted to the Agency and were reviewed by the DBE as shown below:

Sub.#&Date	Firm	Reviewer	DBE Recommendations
P-99-003 1/18/1999 4/26/1999	Mylan	Nouravarsani	A protocol for 2-way crossover BE study and system adhesion. Separate skin irritation study recommended. Study on lowest strength with coadministration of naltrexone. Data on fentanyl OK. No metabolite data was requested.
P-00-012 3/27/2000	Mylan	Nguyen	A revised version of the protocol P-99-003. Firm proposed to use the highest dose of fentanyl, 100 µg/hr, for BE study, instead of the lowest dose (25 mcg/hr). The DBE did not concur with the proposal. Use of lowest strength, 25 mcg/hr, for BE study was recommended (per medical consult).
C-00-346 8/18/2000	Mylan	Fanning	A Clinical control Document: The Medical reviewer recommended that the skin irritation and sensitization potential of this product should be evaluated.
C-00-360 8/30/2000	[redacted]	Chaurasia	A BE control Document: Single-dose, replicate design study on the lowest strength patch (25 mcg/hr) with naltrexone blockade was recommended, along with skin irritation/ sensitization study. Only fentanyl data was requested.
C-00-405 9/27/2000	[redacted]	Chaney	Same as the CD 00-360 with additional question on multiple doses steady-state study. The DBE did not recommend steady-state study but requested only single-dose, replicate design study.
C-01-122 2/27/2001	[redacted]	Shrivastava	Single-dose, replicate design study on the lowest strength patch (25 mcg/hr) with naltrexone blockade. Skin irritation/ sensitization study recommended.
C-01-175 3/26/2001	[redacted]	Nouravarsani	Use 25 mcg/hr strength with narcotic antagonist naltrexone. Replicate study design recommended. FDA considers waiver requests for higher strengths.
C-01-278 5/16/2001	[redacted]	Nouravarsani	This CD was identical to CD 01-175 submitted by [redacted] This CD (C01-175) was submitted by [redacted]
C-01-550 11/08/2001	[redacted]	Shrivastava	Single-dose, 2-way crossover design study on the lowest strength patch (25 mcg/hr) with naltrexone blockade. Skin irritation/ sensitization study recommended.

Note that Mylan has submitted two protocols (Protocol P 99-003 and P 00-012) before the release of the current BA/BE Guidance. The study conducted in the Mylan's submission is based on the Agency's recommendations on those two protocols at that time.

REVIEW OF THE BIOEQUIVALENCE STUDY:

Protocol # FENT-0105

I. IN VIVO FASTING BIOEQUIVALENCE STUDY

A. STUDY INVESTIGATORS AND CONTRACT LABORATORY

This bioequivalence and wear study was conducted at [redacted] The study investigators were [redacted]

B. INFORMED CONSENT AND IRB APPROVAL

The clinical portion of this study was conducted in compliance with the Institutional Review Board regulations in 21 CFR § 56 and Informed Consent regulations in 21 CFR § 50. A copy of the protocol, Form FDA 1572, curriculum vitae, informed consent and IRB review and approval are provided in the Clinical Report in Attachment 4 pages 12 through 82 of the bioequivalence report.

C. STUDY OBJECTIVE

The objective of this study was primarily to investigate the bioequivalence and secondly to compare the wearability (adhesion) and acute irritation of Mylan fentanyl transdermal system to Duragesic®-25 following a single 25 µg/h application worn for 72 hours.

D. STUDY DESIGN

This study was designed as an open-label, randomized, two-treatment, two-period, single-dose, crossover bioequivalence and wear study.

E. SUBJECT SELECTION CRITERIA

40 healthy, adult, non-smoking, volunteers were enrolled from the general population with the intent to complete thirty-six (36) subjects. Subjects who failed to complete the study ("Drop-outs") were not replaced.

Subjects characteristics:

Age	(%)	Weight		Race	(%)	Sex	(%)
< 18	0	Mean	166.1 lbs	Caucasian	29 (72.5%)	Male	33 (82.5%)
18 – 40	33 (82.5%)	Range	123–215 lbs	African- Amer.	8 (20%)	Female	7 (17.5%)
41 – 60	7 (17..5%)			Asian Pacific	1 (2.5%)		
Range	18-53			Hispanic	2 (5%)		

Randomization schedule:

Sequence	Subjects
AB:	**1, 2, 6, 7, 10, 11, 15, 16, 18, 19, 23, 24, 27, 28, 29, 30, 33, 36, 37, 39**
BA:	**3, 4, 5, 8, 9, 12, 13, 14, 17, 20, 21, 22, 25, 26, 31, 32, 34, 35, 38, 40**

F. STUDY SCHEDULE

Subjects were dosed in one enrollment. Subjects were housed from the evening prior to dosing until after the 120 hour blood draw, but were allowed to return to the clinic for the 144 hour blood draw. After a supervised overnight fast (at least 10 hours), each subject received application of a single, 25 µg/h (1 x 25 µg/h) dose of either Mylan fentanyl transdermal system or Janssen Duragesic®-25 worn for three days. Subjects

received a standard meal 4 hours post-dose followed by an evening meal 10 hours after dosing, and at appropriate times thereafter during the housing period. Water was allowed *ad lib* throughout the study. To minimize the opioid effects of fentanyl, ReVia® (naltrexone hydrochloride) 50 mg tablets were administered orally to all subjects 1 hour before each patch application. Additional 50 mg doses were administered every 24 hours, with the last dose given 24 hours after patch removal. Serial blood samples, 7 mL (1 x 7 mL), were collected at the following times relative to dosing: 0, 2.0, 4.0, 8.0, 12, 18, 24, 32, 40, 48, 56, 64, 72 (before patch removal), 76, 80, 84, 88, 96, 108, 120, and 144 hours. Plasma samples were stored in suitably labeled tubes at -70°C ± 15°C until analysis.

All subjects were monitored throughout confinement for adverse reactions to the study formulations and/or procedures, and were released after the 120 hour blood draw but were required to return to the clinic for the 144 hour blood draw. There were at least 7 days between patch removal and application of the next dose. Period 1 was dosed on February 24, 2001 and Period 2 was dosed on March 6, 2001.

For safety, blood pressures, temperature, oxygen saturation, pulse, and respiration rates were measured prior to patch application and at 2.0, 4.0, 8.0, 12, 15, 18, 21, 24, 28, 32, 36, 40, 44, 48, 52, 56, 60, 64, 68, 72, 76, 80, 84, 88, 92, 96, 100, 104, 108, 112, 116, and 120 hours. Patch application was conducted under the supervision of a physician knowledgeable in the continuous administration of potent opioids, in the management of subjects receiving potent opioids for treatment of pain, and in the detection and management of hypoventilation including the use of opioid antagonists.

Transdermal system adhesion was evaluated at each blood collection as follows: 2.0, 4.0, 8.0, 12, 18, 24, 32, 40, 48, 56, 64, and 72 hours post patch application. Skin irritation was evaluated immediately following transdermal system removal and at 0.5, and 1 hour after removal. For subjects who had skin irritation, the skin was evaluated again at 3 and 12 hours after transdermal removal. Continued dermal irritations were evaluated at 12-hour intervals thereafter until resolution of the irritation.

G. DRUG TREATMENTS

Treatment A = Janssen Duragesic® 25 µg/h
25 µg/h (1 x 25 µg/h), Fasting Administration
Lot # : 9910472, Exp. 01/02
Assay Potency: 98.7%

Treatment B = Mylan Fentanyl Transdermal Systems 25 µg/h
25 µg/h (1 x 25 µg/h), Fasting Administration
Lot #: R6J0001, Exp. TBE
Manufacturing Date: January 2001
Theoretical Yield: [redacted] systems
Assay Potency: 101.1%

analytical methods

Redacted 1

Page(s) of trade secret and /or confidential commercial information

A total of —— plasma samples were analyzed for fentanyl. No samples were repeated due to pharmacokinetic anomaly. The firm reported only one (1) sample repeat due to sample lost in process (vial breakage). The reassay value was used as reported value.

Comments on the Analytical Method: The analytical method is acceptable.

2. Clinical

Adverse Events: 35 adverse events were reported in 19 subjects. Among those, 13 events were from the RLD and 22 events were from the test product. Those events were mild in severity, and mostly involved headache, N/V, dizziness, itching at the patch and lightheadedness. No action was taken.

Dropouts: 40 subjects entered the study and 34 completed. 6 subjects did not complete the study for the reasons shown below:

SUBJECT NO.	34	25 and 37	19 and 21	27
REASON	Difficulty tolerating phlebotomy procedures.	Adverse reactions and infection.	Patch falling off	Disruptive behavior
PERIOD	1	1	1	2
REPLACEMENT	N	N	N	N

3) Pharmacokinetic:

Mean (%CV) Plasma Concentrations of fentanyl are given in the following tables.

IN VIVO BIOEQUIVALENCE STUDY #FENT-0105 ARITHMETIC MEAN FENTANYL PLASMA CONCENTRATIONS [ng/mL] VERSUS TIME (CV%) IN 34 SUBJECTS

	Treatment				
	A (Duragesic #9910472)		B (Fentanyl Transdermal System #R6J0001)		B VS A
	Mean (ng/mL)	%CV	Mean (ng/mL)	%CV	P(|T|>t)
Time (hrs)					
0.00 hours	0.00	.	0.00	.	----
2.00 hours	0.01	488.52	0.01	268.01	0.6501
4.00 hours	0.06	134.23	0.10	120.79	0.0080
8.00 hours	0.23	63.71	0.29	62.93	0.0027
12.00 hours	0.34	45.87	0.38	50.09	0.0416
18.00 hours	0.51	43.14	0.52	43.80	0.4871
24.00 hours	0.58	37.79	0.60	41.31	0.4454
32.00 hours	0.51	38.99	0.51	39.07	0.8147

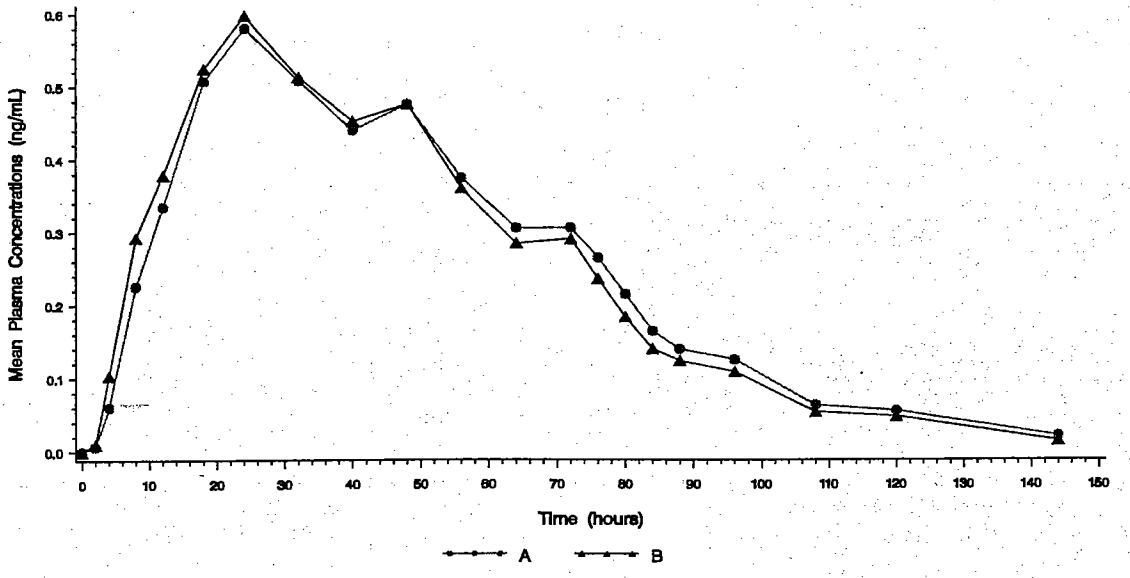
40.00 hours	0.44	29.62	0.45	37.36	0.4439
48.00 hours	0.48	35.08	0.48	38.26	0.9785
56.00 hours	0.37	34.80	0.36	42.53	0.4039
64.00 hours	0.31	34.08	0.28	37.83	0.1219
72.00 hours	0.31	37.12	0.29	37.98	0.2719
76.00 hours	0.26	36.68	0.24	39.84	0.0183
80.00 hours	0.21	41.87	0.18	44.81	0.0023
84.00 hours	0.16	43.33	0.14	51.13	0.0072
88.00 hours	0.14	49.90	0.12	54.66	0.0133
96.00 hours	0.12	52.09	0.11	54.13	0.0069
108.00 hours	0.06	69.93	0.05	70.06	0.0447
120.00 hours	0.06	76.15	0.05	89.22	0.0235
144.00 hours	0.02	136.22	0.01	145.41	0.1339

FENTANYL TRANSDERMAL SYSTEM (FENT – 0105)

Total Dose: 100, Study Type: Fasting

Mean Fentanyl Plasma Concentrations

N = 34



Treatment A is A (Duragesic #9910472)
Treatment B is B (Fentanyl Transdermal System #R6J0001)

MEAN (%CV) FENTANYL PHARMACOKINETIC PARAMETERS IN THIRTY-FOUR HEALTHY SUBJECTS FOLLOWING A SINGLE 25 μg/h (1 x 25 μg/h) DOSE OF FENTANYL TRANSDERMAL SYSTEM WORN FOR THREE DAYS						
Parameter	Arithmetic Mean A = Duragesic®	Arithmetic Mean B = Mylan	LSMEANS Ratio (B/A)		90% Confidence Interval (Log transformed)	
			Firm	Reviewer	Firm	Reviewer
AUCL (ng x hr/mL)	34.91 (32.44)	34.51 (36.07)	0.98	1.02	94% - 103%	97.2% - 106.9%
AUCI (ng x hr/mL)	36.35 (32.42)	35.98 (35.97)	0.98	1.02	94% - 103%	97.4% - 106.5%
CPEAK (ng/mL)	0.601 (34.85)	0.626 (36.49)	1.03	0.97	98% - 110%	91.1% - 102.4%
KEL (hr^{-1})	0.036 (27.56)	0.037 (28.01)				
HALF (hr)	21.02 (28.96)	20.04 (25.87)				
TPEAK (hr)	29.29 (38.47)	27.47 (35.23)				

The reviewer re-ran the SAS ANOVA and recomputed 90% C.I. limits. Although the reviewer's results are slightly different from the firm's results, the 90% C.I limits for AUC and Cmax are within 80% - 125% range.

Conclusion: In-vivo Bioequivalence study acceptable.

II. RESULTS OF THE PATCH ADHESION AND IRRITATION STUDIES

Data on the patch adhesion and irritation studies comparing the test and RLD products were submitted. The Medical Officer has concluded that there is no significant differences among three transdermal systems (Mylan's Fentanyl Transdermal System, Mylan's Placebo Transdermal System and Jansen's (innovator) Transdermal System) in adhesion. Further, the Medical Reviewer has reviewed the irritation study results and has the following recommendations:

1. The FENT-0134 study has PK data and it should be evaluated for bioequivalence.
2. Because of the marked difference in adverse events between the test and reference products, the OGD should determine whether a multidose study is necessary.
3. Also because of the marked difference in adverse events, the OGD should decide whether to request the firm to get its application through the 505(b)(2) mechanism.
4. The firm should conduct a new skin sensitization and irritation study.

The Medical Officer review is electronically attached at the end of this review. Pertinent details from the Medical review are enclosed in the Deficiencies Section of this review and in a letter to the firm.

The DBE responses to the Medical Officer's four recommendations are as follows:

1. The PK data in the FENT-0134 study was reviewed by the Division of Bioequivalence. Since the objective of the study was to evaluate the skin sensitization and irritation by repetitive applications to the skin of normal volunteers, plasma concentrations data were periodically determined to assess the effect of repeated patch application at the same site, not for bioequivalence purposes. Because this study was not intended to determine the bioequivalence of the test and

reference patch, no statistical evaluation was performed and hence no conclusion can be made with respect to the plasma data collected in this study. A cursory review of the data is given below:

This was a clinical study, parallel design in 28 subjects. 14 subjects in each group and treatments were as follows: Group A received: Treatment A (Mylan's fentanyl patch 25 mcg/hr) and Treatment B (Mylan's placebo patch) and Group B received: Treament C (Jansen's fentanyl patch 25 mcg/hr). Each group had a new system applied to the exact same skin location every Sunday, Tuesday and Thursday for 3 consecutive weeks (for a total of 9 consecutive applications). Patches were worn for three days, removed and reapplied repetitively to the same skin site.

Results are tabulated in the table below:

Time	Test (N=14)		Reference (N=14)	
(hrs)	Mean Concentration (ng/ml)	%CV	Mean Concentration (ng/ml)	%CV
-1	0	---	0	---
24	0.703	51.71	0.54	49.03
47	0.549	29.64	0.54	54.00
72	0.767	37.18	0.885	45.81
95	0.598	27.69	0.740	39.61
120	0.818	40.39	1.24	55.20
167	0.491	29.69	0.58	29.21
192	0.929	29.23	1.119	29.65
215	0.660	32.19	0.807	29.21
240	1.259	66.50	1.19	76.90
263	0.749	25.10	0.788	48.17
288	1.096	26.37	1.07	36.25
335	0.415	53.26	0.407	44.27
360	1.08	29.00	2.64	165.04
383	0.791	22.94	1.05	95.78
408	1.119	21.23	1.71	152.39
431	0.854	29.71	0.816	31.86
456	1.219	23.39	1.132	48.22
839	0	---	0.00	374.16
864	0.554	54.51	0.488	40.99

2. Since adverse events were more for the reference patch, a multidose PK/safety study may not be necessary.

3. This application has already been accepted for filing under 505(j)(5).

4. The firm will be requested to conduct a new skin sensitization/irritation study.

III. PRODUCT FORMULATION:

QUANTITATIVE COMPOSITION

FENTANYL TRANSDERMAL SYSTEM, 2.55 mg/6.25 cm²

Composition	Theoretical (6.25 cm²) Quantity/Patch	Theoretical Quantity/ atches
ACTIVE		
Fentanyl	2.55 mg	
INACTIVE		
Silicone Adhesive		
Dimethicone NF		
Component Total		
BACKING		
Polyolefin Film (Mylan Technologies Inc.	6.25 cm²	

IV. IN-VITRO DISSOLUTION TESTING RESULTS:

ANALYTE:	FENTANYL
STRENGTH AND UNIT:	25 mcg/hr
DISSOLUTION METHOD:	
DISSOLUTION MEDIUM:	VOLUME:
DISSOLUTION APPARATUS:	RPM:
ASSAY METHOD:	
DISSOLUTION SPECIFICATION:	

RESULTS OF DISSOLUTION TESTING

Time(hour)	0.5		1		2		8	
UNIT	R6J0001 (Test)	9910472 (Ref)	R6J0001 (Test)	9910472 (Ref)	R6J0001 (Test)	9910472 (Ref)	R6J0001 (Test)	9910472 (Ref)
1								
2								
3								
4								
5								
6								
7								
8								
9								
10								
11								
12								
MEAN	**29.50**	**15.08**	**44.17**	**18.58**	**63.67**	**22.58**	**97.50**	**38.42**
S.D.	1.00	0.79	1.53	0.51	2.27	0.67	1.98	1.31
CV%	3.39	5.26	3.46	2.77	3.56	2.96	2.03	3.41
MIN								
MAX								

V. REQUEST FOR WAIVER OF IN-VIVO BIOEQUIVALENCE:

No waiver request was submitted in this submission.

VI. DEFICIENCIES:

1. The Sponsor has conducted 3 studies and none of them represent an ideal design to test for skin irritation and sensitization potential of the generic transdermal compared to its reference listed product.
In the first study (FENT-0132) comparing the fentanyl placebo patch with a positive control (SLS) and a negative control, the placebo patch was found to be significant less irritating the SLS patch. There were no contact sensitization reactions noted in this study. The study did not include either the test or reference products. Since the active ingredient is contained within the adhesive of the generic transdermal, the placebo patch without fentanyl is not comparable to the patch with the active ingredient. Therefore, the observations in this study on skin irritation and contact sensitization potential cannot be extrapolated to Mylan's transdermal system.
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In addition, the sponsor conducted two studies, one on irritation and a second on sensitization in animals. The recommended studies are to be conducted in humans. The required testing is outlined in the guidance: *Guidance for Industry: Skin Irritation and Sensitization Testing of Generic Transdermal Drug Products, December 1999.* The sponsor did not conduct studies that would comply with the guidance. Due, possibly, to concern over exposing normal volunteers to a potentially habituating drug (fentanyl), the firm used naltraxone blockade of the fentanyl effect. The firm appeared to have been reluctant to the traditional design of applying 2 patches with active drug at the same time in a single patient. Therefore, instead of simultaneously

testing the generic and reference listed drug in the same individual, the firm has chosen to conduct a small parallel group study comparing the two. Despite the small number of patients and because the Duragesic® patch is somewhat irritating, the firm has been able to demonstrate that the generic patch is less irritating than the reference listed drug and that neither cause sensitization. The study is too small to make any conclusions on the contact sensitization potential and the observed differences in skin irritation have not been analyzed by the FDA statistician. Hence, data on assessing skin irritation and sensitization and patch adhesion are incomplete. The firm is requested to submit a new skin irritation/sensitization study using a parallel design and a sample size adequate to assess the potential for contact sensitization, for evaluation. Please refer to the Agency's guidance: *Guidance for Industry: Skin Irritation and Sensitization Testing of Generic Transdermal Drug Products, December 1999* for more information. This guidance is available on the internet at: http://www.fda.gov/cder/guidance/index.htm

2. The dissolution testing conducted by the firm is incomplete. The firm is requested to conduct dissolution testing on 12 individual dosage units for the test and reference products. Dissolution testing should be conducted in different media ([redacted] , and multipoint dissolution profiles should be obtained using discriminating agitation speed. A surfactant may be used with appropriate justification. Adequate sampling times should be performed (See current USP Sections <711> and <724> for general dissolution requirements.
3. Please indicate how [redacted] was prepared. The USP indicates that pH of the [redacted] cannot go below [redacted]. See USP 24 page 2232).
4. Study FENT-0134 contains some pharmacokinetic data. In order to evaluate those data, the firm is requested to calculate appropriate pharmacokinetic parameters and statistically compared PK parameters of the test and RLD.
5. Firm should submit all analytical SOPs including the one for sample repeats.

VII. RECOMMENDATION:

This submission submitted by Mylan is incomplete per Deficiencies above. The firm should be informed of the Deficiencies.

Nhan L. Tran, Ph.D.
Review Branch II

RD INITIALLED SNERURKAR
FT INITIALLED SNERURKAR 4/4/2002

Concur: Date: 4/8/02
Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence

CC: ANDA 76-258 (original), HFD 655 (Tran, Nerurkar), Drug File, Division File

CC: ANDA
ANDA DUPLICATE
DIVISION FILE
FIELD COPY
DRUG FILE

Endorsements: (Draft and Final with Dates)
HFD-655/Reviewer
HFD-655/Bio Team Leader
HFD-617/Project Manager
HFD-650/Dale Conner 4/16/02

BIOEQUIVALENCY - DEFICIENCIES

Submission Date:
September 20, 2001

1. **FASTING STUDY** (STF) Strengths:25 mcg/hr
Clinical:
Analytical: **Outcome: AC**

2. **DISSOLUTION DATA** (DIS) Strengths: 25 mcg/hr
Outcome: IC

3. **OTHER (Skin irritation, patch adhesion studies)** Strengths: 25 mcg/hr
Outcome: IC

Outcome Decisions: **IC** - Incomplete

WinBio Comments

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

76-258

ADMINISTRATIVE DOCUMENTS

T-con mtg

Redacted 2

Page(s) of trade secret and /or confidential commercial information

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE : October 30, 2001

TO : Director
Division of Bioequivalence (HFD-650)

FROM : Chief, Regulatory Support Branch
Office of Generic Drugs (HFD-615)

10/30/2001

SUBJECT: Examination of the bioequivalence study submitted with an ANDA for Fentanyl Transdermal System, 0.6 mg/24 hr, to determine if the application is substantially complete for filing and/or granting exclusivity pursuant to USC 355 (j)(5)(B)(iv).

Mylan Technologies, Inc. has submitted ANDA 76-258 for Fentanyl Transdermal System, 0.6 mg/24 hr.
The ANDA contains a certification pursuant to 21 USC 355 (j)(2)(A)(vii)(iv) stating that patent(s) for the reference listed drug will not be infringed by the manufacturing or sale of the proposed product. Also it is a first generic. In order to accept an ANDA that contains a first generic, the Agency must formally review and make a determination that the application is substantially complete. Included in this review is a determination that the bioequivalence study is complete, and could establish that the product is bioequivalent.

Please evaluate whether the study submitted by Mylan on October 12, 2001 for its Fentanyl product satisfies the statutory requirements of "completeness" so that the ANDA may be filed.

A "complete" bioavailability or bioequivalence study is defined as one that conforms with an appropriate FDA guidance or is reasonable in design and purports to demonstrate that the proposed drug is bioequivalent to the "listed drug".

ANDA 76-258

In determining whether a bio study is "complete" to satisfy statutory requirements, the following items are examined:

1. Study design

   (a) Appropriate number of subjects
   (b) Description of methodology

2. Study results

   (a) Individual and mean data is provided
   (b) Individual demographic data
   (c) Clinical summary

The issue raised in the current situation revolves around whether the study can purport to demonstrate bioequivalence to the listed drug.

We would appreciate a cursory review and your answers to the above questions as soon as possible so we may take action on this application.

DIVISION OF BIOEQUIVALENCE:

Concur Barbara M. Scott 11/2/01

✓ Study meets statutory requirements

_____ Study does **NOT** meet statutory requirements

Reason:

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ON ORIGINAL

Director, Division of Bioequivalence

11/8/01
Date

Dale:

Mary has raised some issues regarding the differential adverse events observed between the two products and has made some suggestions (see page 8 of the review, Section II, comment # 2 and #3). Her comments are both scientific and regulatory.

I believe if a generic product complies with the Agency's statutory requirements for a 505(j) application and meet the preset standard of bioequivalence we would treat it as such. Although DBE considers and reviews adverse events in all BE studies, such observations have not been one of the parameters for BE documentation. We have seen differences in the number and type of adverse events between the two products in many BE studies. While DBE evaluates these as observations, In many studies the test product shows equal, lower, and in some cases, higher number of adverse events compared to the RLD. We evaluate these observations carefully and do not use it as a BE measure, unless there is some safety issue is suspected. In this case, the test product performs better than the RLD.

I have not signed the review yet. I am bringing this to your attention before we get it out of DBE as Mary has made the comments. I am comfortable about the position DBE is taking.

Rabi
3/26/2002

APPEARS THIS WAY
ON ORIGINAL

4.1
WAIVE, 7AD

RECORD OF TELEPHONE CONVERSATION

I called the firm and left a voice mail massage to Dr. Brochu requesting that the word "_____' should be deleted from the "Cardiac Disease" subsection, PRECAUTIONS to read "Fentanyl may produce…". I asked to revise the labeling as above and submit in FPL as an amendment to this application.

Chan

V:\FIRMSAM\MYLAN\TELECONS\76258July 19.2002.doc

APPEARS THIS WAY ON ORIGINAL

DATE 7/19/02
ANDA 76-258
IND NUMBER
TELECON
INITIATED BY _ APPLICANT/ SPONSOR MADE X BY TELE.
X FDA _ IN PERSON
PRODUCT NAME Fentanyl Transdermal System
FIRM NAME Mylan Tech. Inc.
NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD W.E. Brochu, Ph.D.
TELEPHONE NUMBER 802-527-7792, ext 426
SIGNATURE

FDA CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANESTHETIC, CRITICAL CARE, AND ADDICTION DRUG PRODUCTS
HFD-170, Room 9B-45, 5600 Fishers Lane, Rockville MD 20857 Tel:(301)827-7410

File 76-258

MEMORANDUM

DATE: 8/15/02

TO: Harvey Greenberg, Consumer Safety Officer, Office of Generic Drugs, RSB, (HFD-615)

THROUGH: Bob Rappaport, M.D., Team Leader, Deputy Division Director DACCADP, CDER 8/15/02

THROUGH: Cynthia McCormick, M.D., Director DACCADP, CDER Cynthia McCormick MD 8/20/02

FROM: Sharon Hertz, M.D., Medical Officer, (HFD-170)

RE: Mylan Transdermal Fentanyl, ANDA 76-258 LRupper 8/22/02

Reason for Consult: OGD has requested DACCADP evaluate the skin sensitization protocols for a generic fentanyl transdermal patch with regard to the amount of fentanyl exposure and subject safety.

Recommendations: Due to the very high fentanyl levels demonstrated following repeated patch application to the same site using the 25 ug/h patch doses of both the innovator, Duragesic, and the study product, future studies utilizing repeated same-site application of the 25 ug/h dose or higher can not be considered safe to proceed. This determination is based on the information provided from Study FENT-0134. The description of symptoms of opioid activity and withdrawal, were exhibited by subjects in spite of premedication with naloxone, and the report of markedly elevated fentanyl levels in several patients, demonstrate that the opioid antagonism by naloxone was inadequate to fully protect the subjects.

Background: The sponsor is developing a generic transdermal fentanyl delivery system. This patch differs from Duragesic, the only currently approved fentanyl transdermal patch in that while Duragesic has a drug reservoir covered by a rate limiting membrane, the proposed generic will have a fentanyl containing silicone adhesive layer. The sponsor has conducted three skin

sensitization studies but has been informed by the Office of Generic Drugs that additional testing is required to be in compliance with the current Agency guidance for such testing.

A consult dated 10/22/00 by this Reviewer, advised that the use of active fentanyl patches of 25 ug/hr in normal volunteers was dangerous due to the risk of opioid overdose and the development of physiological opioid dependence. The use of naltrexone blockade or opioid tolerant patients was recommended.

According to the Office of Generic's Medical Officer Review of the study results dated 1/24/01 provided with this consult, two of the clinical skin sensitization studies utilized a placebo transdermal system, (Studies FENT-0132 and FENT-0133) and the third study, FENT-0134, utilized an active Mylan fentanyl transdermal system and an active Duragesic patch. Naltrexone blockade (100 mg/day) was utilized in Study FENT-0134 to avoid exposing opioid naïve, normal volunteers to levels of fentanyl known to be potentially unsafe in such subjects. Additionally, to reduce the risk of opioid-related adverse events, rather than the usual method of applying both the active study drug and the approved comparator concurrently, subjects received only one of the two treatments. Thirty-two subjects were enrolled and 28 subjects completed the study. Only one of the drop-outs was related to adverse events, nausea and vomiting requiring treatment with an antiemetic. There were many adverse events reported, overall more among subjects who received Duragesic than the Mylan product, and many attributable to opioid exposure or opioid withdrawal.

The conclusion of this review was that the studies provided were inadequate in characterizing the differences between the test and reference transdermal products, and also raised the question of a lack of bioequivalence given the differences in adverse event reporting between the two groups. An additional study using a larger sample size was recommended along with a PK assessment of systemic exposure and careful assessment of AEs.

The current submission represents the sponsor's request for reconsideration of the need for further studies. The sponsor presents an argument for why the completed studies are sufficient. The sponsor expresses concerns about the safety of exposing normal volunteers to the fentanyl, and indicates that the inactive components in the product are widely used in topical and transdermal pharmaceutical products with already-known sensitization and irritation potentials.

In the event that the sponsor's arguments against further studies were not accepted, the sponsor has provided proposals for two studies. Study FENT-0249, a parallel-design study focusing on sensitization potential incorporates a rotation of skin sites for serial patch applications, with the intent of minimizing the potential for excessive irritation and resultant potentially dangerous fentanyl plasma levels. Alternatively, if asked for additional data assessing cumulative irritation and sensitization potential, the sponsor has submitted a proposal for FENT-0252. This protocol describes successive same-site patch applications.

Title: Evaluation of Contact Sensitization Potential of Fentanyl Transdermal System in Normal Healthy Volunteers. FENT-0249

Objective: Comparison of Mylan fentanyl transdermal system and Duragesic with respect to induction of contact sensitization by repetitive applications, and to evaluate patch adherence and primary irritation.

Study Design: Randomized, open-label, parallel study

Study Duration: 5 weeks, two days

Study Population: N=400 healthy adults

Inclusion Criteria:
1. Male and female, ≥ 18 years of age
2. Adequate birth control
3. Signs of withdrawal following naltrexone administration 24 hours prior to test system

Exclusion Criteria:
1. Pregnant or lactating
2. Use of any medication including OTC products for14 days prior.

Conduct of Study:
- Study drug: Duragesic 25 ug/h
  Mylan fentanyl 25 ug/h transdermal system
- Subjects will have new test systems applied to a different skin location every Monday, Wednesday for 48 hours, and Friday for 72 hours, for three consecutive weeks.
- After the three-week induction phase, there will be a 2-week rest period followed by a 48 hour application to a contralateral location (challenging the sensitization ability of the test system.
- Naltrexone 100 mg will be administered daily starting one day preceding patch placement, during the first 4 days and the last day of the 2 week rest phase, daily during the challenge phase and for 3 days following study drug removal.
- Subjects will remain at the study site for 24 hours following first patch application, then return to the site each morning for naltrexone dosing of 100 mg through day 25
- Subjects will return on day 35 for the challenge patch and receive naltrexone on day 35 prior to the rechallenge, and through 72 hours after patch removal. Subjects will remain at the study site for the 72 hours after patch application.
- Skin reaction evaluations will be performed by a trained and blinded observer at 30 minutes, and at 24, 48 and 72 hours following removal of the challenge phase transdermal system.
- Pulse oximetry will be performed with vitals while subjects are confined to the clinical site.
- LFTs will be measured weekly
- Subjects experiencing hypoventilation will be observed until stabilized.

Title: Evaluation of Contact Sensitization and Cumulative Irritation Potential of Fentanyl Transdermal Systems in Normal Healthy Volunteers, FENT-252

Objective: Comparison of Mylan fentanyl transdermal system and Duragesic with respect to induction of contact sensitization by repetitive applications, and to evaluate patch adherence and primary irritation.

Study Design: Open-label, parallel, single period sensitization study

Population: N=400 healthy volunteers

Conduct of Study:

- Treatment groups:
  Mylan fentanyl 25 ug/h transdermal system and placebo of this system
  Duragesic 25 ug/h
- The study will proceed as above except two areas of the deltoid region of the same arm will be designated for patch application. For the Duragesic-only group, one area will remain open, but marked to retain rater blinding.
- The initial assignment of the test systems to a specific area will be rotated to eliminate position bias.

Comments:

If required to provide additional skin sensitization information, the sponsor has indicated a preference to perform Study FENT-0249 which proposes to rotate the patch site. The sponsor has provided a protocol for Study FENT-0252 which proposes repeated patch administration to the same site, but is reluctant to conduct this study. Given the information available from FENT-0134, Study FENT-0252 does not appear sufficiently safe to proceed.

The reporting of adverse events during FENT-0134 suggestive of direct opioid effects (nausea, vomiting) and of opioid withdrawal (abdominal cramping, diarrhea, sweating, shakiness, insomnia) is concerning. These adverse events were more frequent from the Duragesic group, but some were also present from the Mylan product group. Neither group should have experienced these adverse events given the planned dosing with naltrexone. The details of the protocol are not available for review at this time, but according to the review conducted by Dr. Fanning, patches were reapplied to the same site unless maximum irritation was found. According to an excerpt from the final study report provided with the new protocol package, fentanyl levels of [redacted] were reported from four subjects, three of whom received Duragesic patches, and one the Mylan patch.

The reported fentanyl levels following repeated dosing with a 100 ug/hr patch (applied to different sites) ranged from 0.5 to 4.5 ng/ml during studies reported in the Duragesic product label. The mean fentanyl level following single 72-hour applications of the 25 ug/hr patch was 0.6 ng/ml with a standard deviation of 0.3. The Duragesic label instructs the patient to apply the patch to non-irritated skin, and to change the site for the next system application.

The reporting of symptoms consistent with opioid effects following repeated same-site administration of the Duragesic and Mylan patches suggests that at least some of the fentanyl levels attained were high enough to overwhelm the opioid blockade offered by naltrexone. The differences in frequency of these adverse events between the Duragesic and Mylan patches may

have been due to a either difference in bioequivalence, or alternatively, reflected a greater degree of enhanced bioavailability due to local skin irritation. The Duragesic group exhibited more skin irritation, and this may have been responsible for higher fentanyl levels and the more frequent adverse events.

There are several options to consider to make the future studies safer. The naltrexone dose could be increased in an attempt to further block the mu opioid receptors. However, there is little data to provide information about how much additional protection to the subjects would be offered by increasing the naltrexone dose, or how much additional naltrexone over the over 100 mg/day would be sufficient. Another option would be to rotate the patch application sites as proposed in Study FENT-0249. This should lead to more predictable fentanyl levels that would be more adequately blocked by the naltrexone, but may not provide as much information about local sensitization. Alternately, a smaller patch size could be considered. As the Mylan product consists of the fentanyl in the adhesive, smaller sizes can be constructed by cutting the patch. Given the plasma levels provided, a patch size that delivers 2.5 ug/hr, one tenth of the previously studied patch size, would provide a safety margin for blood levels of one order of magnitude. Anticipating a maximum level of approximately 1.6 ng/ml, the naltrexone dose of 100 mg/day should be adequate. However, this manner of dose reduction is not possible for the Duragesic patch, the smallest marketed size is the 25 ug/hr patch. The Duragesic patch consists of a drug reservoir separate from the adhesive and is a design that can not be cut to reduce the size. Given the altered pharmacokinetics of the Duragesic patch following repeated same-site application, even the use of opioid tolerant patients may not be safe.

Of historical note, formal skin irritation studies were not submitted in the Duragesic NDA. In a letter to Dr. Robert Temple dated August 19, 1988 referencing prior interactions between Alza and the Agency, the sponsor notes that during a discussion on June 23, 1983, agreement was reached that skin irritation studies would not be performed. From this letter, "Since fentanyl is a narcotic, studies cannot be done in volunteers, except where the drug is indicated for symptom control, therefore irritation studies could be done as a part of the observations on analgesia." Naltrexone was not been approved for marketing until 1984.

There is a new formulation of Duragesic under development by Janssen, D-Trans. This is an fentanyl in adhesive formulation. The new formulation is similar to Duragesic, but lacks a permeation enhancer. The sponsor had submitted two protocols to evaluate skin sensitization. Protocol C-2000-019-00 was an open-label study to evaluate contact sensitization. A consult from DDDDP dated 2/6/01 commented that open label studies are not considered adequate, that a positive and negative control would be needed in a double-blind study of irritation. Use of the placebo would be acceptable if Duragesic had been adequately tested for contact sensitizing potential. At least 200 subjects should be enrolled. If positive sensitization occurred in the challenge phase, the individual ingredients should be tested to identify the sensitizing agent. Protocol C-2000-020-00 was a double-blind study to evaluate the phototoxicity potential. The consultant commented that use of a 2.5 ug/hr system as proposed would be inadequate given the intended production of 100 ug/hr systems. A phototoxicity study would be needed only if the active ingredient had appreciable UVA or UVB absorption, and if so, at least a 25 ug/h product should be used. Subsequently, two single dose protocols were submitted to explore the PK of the

100 ug/h patch in different skin types with the sponsor noting skin site reactions would be assessed during these studies.

APPEARS THIS WAY
ON ORIGINAL

PAGE(S) HAVE BEEN REDACTED IN FULL FROM THIS DOCUMENT

REASON:

_____ b(2) 'low'

_____b(4) CCI

_____b(4) TS

__6__b(5) Deliberative Process; Attorney Client and Attorney Work Product Privilege

_____b(6) Personal Privacy

_____b(7) Law Enforcement Records

Wang, Tao Chin L

From: Hixon, Dena R
Sent: Friday, January 31, 2003 7:52 AM
To: Conner, Dale P; Fang, Florence S; West, Robert L
Cc: Kim, Carol Y; Scardina, Krista
Subject: Mylan Fentanyl application

Folks,

Back at the end of the summer when we made recommendations to firms about skin sensitization and irritation (and patch adhesion) testing for fentanyl transdermals, we reviewed the studies that Mylan had done and were satisfied that they had adequately tested their patch and that it was as good as the innovator for both adhesion and for irritation/sensitization. However, in light of our recent discussion about the Mylan Estradiol patches and the apparent association between aging patches and poor adhesion, I wonder if we shouldn't re-visit the patch adhesion issue for this product also and ask for studies on older patches.

Hopefully the reviewing chemist knows whether the adhesive used for the fentanyl patch is the same as that used for the estradiol patch. Do I recall correctly that the firm has reformulated the estradiol patches? We need to be sure that we are comfortable with older patches from the adhesion perspective and that the to-be-marketed formulation is the same as that used for the skin sensitization/irritation/adhesion testing. The fentanyl patch is to be worn for 72 hours, not 7 days, so the problem may not be as apparent, but if aging patches dont stick as well, we could have a similar TIACC problem with these.

Any advice or comments will be appreciated.
Thanks,
Dena

Wang, Tao Chin L

From: Fang, Florence S
Sent: Friday, January 31, 2003 10:23 AM
To: Wang, Tao Chin L; Basaran, Sema; Mirzai Azarm, Bita
Cc: Smith, Glen J; Venkataram, Ubrani V; Rosencrance, Susan M; Sayeed, Vilayat A; Cai, Bing; Liu, Shing Hou; Patel, Rashmikant M; Schwartz, Paul
Subject: Fentanyl TDS

Tao-Chin:

Mylan's Estradiol TDS (Bing Cai's ANDA) raised the issue of skin adhesion of aged patches, which may directly affect product performance.

We have seen for Bita's Elan clonidine TDS, there is a significant change in adhesive data (peel, tack and adhesion) over 24-month room temperature stability testing while accelerated data showed a relative small change.

Dena has indicated her concern with Mylan's Fentanyl TDS (see attached email). Please take a good look of the Fentanyl TDS (ANDA 76-258) stability data for the adhesive tests. You can copy the appropriate pages of the submission for this purpose. Please also let us know the adhesive material(s) and the specifications used for the TDS, so that we can compare across applications.

Sema and Bita: We would like to ask you to give us the same data (adhesive material specification and stability data) for your ANDA for clonidine TDS.

I hope you can have the information to me by Tuesday, 2/4/03.

Thank you,

Florence

Mylan Fentanyl application

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ON ORIGINAL

Wang, Tao Chin L

From: Fang, Florence S
Sent: Wednesday, February 05, 2003 6:12 PM
To: Hixon, Dena R
Cc: Kim, Carol Y; Scardina, Krista; Conner, Dale P; West, Robert L; Wang, Tao Chin L; Mirzai Azarm, Bita; Basaran, Sema; Cai, Bing; Venkataram, Ubrani V; Rosencrance, Susan M; Smith, Glen J; Liu, Shing Hou; Patel, Rashmikant M; Schwartz, Paul; Sayeed, Vilayat A
Subject: RE: Mylan Fentanyl application

Dena:

Mylan's Fentanyl system (76-258) consists of a backing, drug adhesive matrix (fentanyl,) and a release liner.

At this time there is limited data on adhesive properties. Mylan has submitted tack test using a standard stainless steel probe. The values run from at initial to at 12-month. These numbers are average of 6 readings (no RSD given). Mylan did not include in its specification.

As expected, there is indication adhesive properties change with ageing. The difficulty is how to interpret and correlate the in vitro data to in vivo product performance (adhesion to skin) for the fentanyl patch as for the other TDS products.

Applicants come up with different patch design and use different types of dhesive depending on the drug to be delivered and the delivery duration.

[ ]

I understand TDS will be the subject of a brown bag and ANDA review forum. We will be hearing more in coming weeks!

Florence

-----Original Message-----
From: Hixon, Dena R
Sent: Friday, January 31, 2003 7:52 AM
To: Conner, Dale P; Fang, Florence S; West, Robert L
Cc: Kim, Carol Y; Scardina, Krista

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

76-258

CORRESPONDENCE

MYLAN TECHNOLOGIES INC.

Mr. Gary Buehler
Director, Office of Generic Drugs
CDER (HFD600)
Food and Drug Administration
Metro Park North II
Room 150
7500 Standish Place
Rockville MD 20855-2773

MINOR AMENDMENT
LABELING

ANDA 76-258

FENTANYL TRANSDERMAL SYSTEM,
25mcg/hr, 50mcg/hr, 75mcg/hr, and 100mcg/hr

DATE: November 20, 2003

ORIG AMENDMENT
N/AF

Dear Mr. Buehler:

Reference is made to Mylan's pending ANDA for fentanyl transdermal system (FTS) identified above, to a labeling amendment to this application dated 6/20/02, and to an e-mail correspondence dated 11/20/03 from Mr. Chan Park of the FDA's Office of Generic Drugs, to Mr. Frank Sisto of Mylan Laboratories, Inc.

This amendment provides Final Printed Labeling (FPL) for the prescribing information and patient information leaflet for FTS. This labeling reflects the recently approved changes to Duragesic labeling (pediatric patient population) and the guidance provided by Mr. Park on 11/20/03. We are providing three (3) copies of this submission: archival and review copies each containing twelve (12) copies of the FPL, and a desk copy for Mr. Chang containing one (1) copy of the FPL.

We note that FPL for the patch, pouch, and carton labeling were submitted in our amendment of 6/20/03. Those items reflected prior Agency comments and were not affected by recent changes in the prescribing information that is the subject of this amendment.

Should you require additional information or have any questions regarding this amendment, please contact the undersigned at (802) 527-7792, ext. 426 or via facsimile (802) 527-8155.

Sincerely,

W.E. Brochu, Ph.D.
Vice President, Regulatory Affairs and Quality

RECEIVED
NOV 2 1 2003
OGD/CDER

Desk Copy: Mr Chan Park

MYLAN TECHNOLOGIES INC.

(NAM)
ORIG AMENDMENT

Mr. Gary Buehler
Director, Office of Generic Drugs
CDER (HFD600)
Food and Drug Administration
Metro Park North II
Room 150
7500 Standish Place
Rockville MD 20855-2773

Telephone Amendment
ANDA# 76-258

Fentanyl Transdermal System: 25mcg/hr, 50mcg/hr,75mcg/hr, and 100mcg/hr

October 24, 2003

Dear Mr. Buehler:

Reference is made to our ANDA #76-258 and to a telephone amendment requested by Dr. Smith and Mr. Palate on 10/21/03.

Mylan hereby submits a complete response to the reference request. This amendment includes a modification of the viscosity specification for BioPSA 7-4201, the adhesive used in the manufacture of our Fentanyl Transdermal System along with the requested justification for that specification. We have additionally changed the name associated with this material to correspond to the change in name made by the supplier.

We certify that as required by 21 CFR 314.96(b) a true copy of this submission has been provided to FDA's New England District Office.

As requested this amendment is being submitted by facsimile and followed by hard copy. Please advise if there any questions related to this submission or application.

Sincerely,

W.E. Brochu, Ph.D.
Vice President Regulatory Affairs and Quality

RECEIVED
OCT 27 2003
OGD/CDER

NAF
8-18-2003
GM

MYLAN LABORATORIES INC.

(Sent via facsimile on August 8, 2003)

August 8, 2003

GENERAL CORRESPONDENCE
(Request for Issuance of ANDA Approvable Letter)

Office of Generic Drugs, CDER, FDA
Gary J. Buehler, Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

NEW CORRESP
NC

RECEIVED
AUG 11 2003
OGD/CDER

RE: FENTANYL TRANSDERMAL SYSTEM, 25µg/hr, 50µg/hr, 75µg/hr, and 100µg/hr
ANDA 76-258

Dear Mr. Buehler:

The purpose of this correspondence is to request that OGD consider issuance of an approvable letter for Mylan's ANDA 76-258, pertaining to Fentanyl Transdermal System, 25, 50, 75 and 100µg/hr. This ANDA, which is currently pending approval, represents a potential first generic entry for a bioequivalent product to Duragesic® and affords Mylan with a first to file opportunity regarding this generic drug product. Also, since Mylan was not sued with regard to its paragraph IV patent certification within the statutory 45-day period, approval of this ANDA can be granted when the Agency has successfully completed the application review process. Information to support that Mylan was not sued within the 45-day period was previously submitted to this ANDA on February 5, 2002. The understanding that we were first to file is based on the fact that we have been unable to find any evidence of either another ANDA filing for this product being submitted prior to Mylan's application or documentation that any litigation was initiated by the NDA and patent holder against any company prior to the date litigation commenced against Mylan.

The approval of Mylan's Fentanyl Transdermal ANDA will not be delayed by the award of pediatric exclusivity to Alza beyond the expiration of United States Patent Number 4,558,580. Since Alza failed to bring suit within 45 days of receipt off Mylan's paragraph IV certification, it therefore failed to trigger the 30-month stay under 21 U.S.C. Section 355(j)(5)(B)(iii). In this situation, Hatch-Waxman dictates that Mylan's ANDA shall be effective immediately. In particular, section 505(j)(5)(B)(iii) states that:

> If the application made a certification described in subclause (IV) of paragraph (2)(A)(vii), **the approval shall be effective immediately unless** an action is brought for infringement of a patent which is the subject of the certification before the expiration of forty-five days from the date the notice provided under paragraph (2)(B)(i) is received.
>
> See: 21 U.S.C. Section (emphasis added).

P.O. Box 4310 • 781 Chestnut Ridge Road • Morgantown, West Virginia 26504-4310 U.S.A. • (304) 599-2595 • FAX (304) 599-7284

It is obvious that Mylan would like to obtain approval of its Fentanyl ANDA as soon as possible. However, we understand that there is in issue relating to pediatric labeling under the BPCA that is outside of our control that could delay the final approval of this ANDA. Because of this issue, we would like to gain "Approvable" status pending finalization of the BPCA labeling issue. To the best of our knowledge there are two outstanding issues which could preclude immediate approval of ANDA 76-258. The first involves completion of the review of our April 5, 2003 minor amendment which addresses all outstanding CMC issues pertaining to our application. As of July 25, 2003, it was our understanding that the primary review of this amendment had been completed with a positive outcome and had been forwarded to the chemistry team leader for the secondary review prior to recommendation for approval. As the secondary review was anticipated to take approximately a week to complete, this aspect of the review process should now be resolved.

The remaining issue is finalization of the package insert labeling to incorporate required BPCA revisions pertaining to a new pediatric exclusivity awarded to the NDA holder. Except for the inclusion of the required BPCA carve out language to address the new pediatric exclusivity, Mylan believes it has addressed and responded to all of the Agency's comments pertaining to labeling. In the past, when the only remaining issue for the Agency to resolve is outside the applicant's control, the Agency has issued an "Approvable" letter to the applicant. This has occurred most recently in the specific instances when the only issue was the Agency's need to internally resolve the appropriate pediatric carve out and the additional associated language related to the carve out or other instance where there was a labeling issue that the Agency needed to internally resolve that was outside of the applicant's control. Examples include the issuance of "Approvable" letters for Metformin, Gabapentin, Ticlopidine and Tramadol.

We have been informed that the process for internal CDER evaluation of the pediatric carve out pertaining to the Fentanyl labeling will be a rather lengthy process involving review by the applicable New Drug Review Division, the Pediatric Labeling Review Team and Office of Chief Counsel. We believe it is unfair for the Agency to withhold an important action for an applicant if the applicant has indeed met all appropriate requirements and the final approval decision is being withheld to permit the Agency sufficient time to resolve the issue related to the BPCA carve out. By requesting issuance of an "Approvable" letter Mylan is not asking the Agency to do anything it has not done in other similar circumstances. The issuance of an "Approvable" letter, as mentioned above, is consistent with the situation where the Agency has found all of an applicant's submissions satisfactory and the Agency is resolving an issue outside of the applicant's control (in this case the BPCA required pediatric carve out language). In addition, Mylan is currently in litigation with the patent holder (outside of the Hatch-Waxman provisions, as the NDA/patent holder did not file suit within the required 45-day period). The issuance of an "Approvable" letter could place Mylan in a much stronger position in the litigation process.

We appreciate your time in considering our request and look forward to a positive outcome. Please feel free to contact me at (304) 599-2595, ext. 5243 should you wish to discuss this issue further or need additional information.

Regards,

John P. O'Donnell, Ph.D.
Chief Scientific Officer
Mylan Laboratories

MYLAN TECHNOLOGIES INC.

NEW CORRESP

Dr. Gary Buehler
Director, Office of Generic Drugs
CDER (HFD600)
Food and Drug Administration
Metro Park North II
Room 150
7500 Standish Place
Rockville MD 20855-2773

ANDA # 76-258

Fentanyl Transdermal System, 25µg/hr, 50µg/hr, 75µg/hr, and 100µg/hr

Patent Amendment

Date: July 31, 2003

Dear Dr. Buehler:

Reference is made of our ANDA 76-258 for Fentanyl Transdermal Systems 25µg/hr, 50µg/hr, 75µg/hr, and 100µg/hr. Enclosed please find a revised patent amendment related to recently granted exclusivities for Duragesic, the reference listed drug.

Please advise if there are any questions related to this amendment.

Sincerely,

W.E. Brochu, Ph.D.
Vice President, Regulatory Affairs and Quality

RECEIVED
AUG 0 1 2003
OGD/CDER

G:\Reg_Affrs\Juliane\ANDAS\Fentanyl\Amendments\Patent Amendment-2_7-31-03.doc

MYLAN TECHNOLOGIES INC.

ORIG AMENDMENT

N/AF

Mr. Gary Buehler
Director, Office of Generic Drugs
CDER (HFD600)
Food and Drug Administration
Metro Park North II
Room 150
7500 Standish Place
Rockville MD 20855-2773

MINOR AMENDMENT
LABELING

ANDA 76-258

FENTANYL TRANSDERMAL SYSTEM, 25mcg/hr, 50mcg/hr, 75mcg/hr, and 100mcg/hr

DATE: June 27, 2003

Dear Mr. Buehler:

Reference is made to Mylan's pending ANDA for fentanyl transdermal system (FTS) identified above, and to telephone correspondence with Mr. Chan Park in the Division of Labeling and Program Support on 6/17/03 and 6/26/03.

This amendment provides proposed revised prescribing information and patient information leaflet for FTS. This labeling was revised in response to the recently approved changes to Duragesic labeling (pediatric patient population).

As requested by Mr. Park, the proposed labeling is submitted as a side-by-side comparison of the new Duragesic and proposed generic product labeling for Mylan's FTS. We are providing 2 copies, one archival and one for review purposes. Under separate cover, we are providing a desk copy directly to Mr. Park as he requested.

Should you require additional information or have any questions regarding this amendment, please contact the undersigned at (802) 527-7792, ext. 426 or via facsimile (802) 527-8155.

Sincerely,

W.E. Brochu, Ph.D.
Vice President, Regulatory Affairs and Quality

Desk Copy: Mr Chan Park

RECEIVED
JUN 30 2003
OGD/CDER

MYLAN TECHNOLOGIES INC.

ORIG AMENDMENT
AMENDMENT
NDAM

Mr. Gary Buehler
Director, Office of Generic Drugs
CDER (HFD600)
Food and Drug Administration
Metro Park North II
Room 150
7500 Standish Place
Rockville MD 20855-2773

MINOR ANDA Amendment

ANDA# 76-258

Fentanyl Transdermal System
25 mcg/hr, 50 mcg/hr,
75 mcg/hr, and 100 mcg/hr

April 5, 2003

Dear Mr. Buehler:

Reference is made to ANDA 76-258 for Fentanyl Transdermal System and to the Agency's letter of 4/1/03.

This amendment provides complete responses to the Agency's comment letter of 4/1/03. We believe our responses are consistent with the available data and fully meet the Agency's expectations for the changes in specifications that have been requested.

Mylan hereby certifies that pursuant to 21 CFR 314.96(b), a true copy of this amendment has been provided to FDA's New England District Office.

Finally, we request that if there are any further comments or questions related to this application that we be provided with the opportunity to discuss these directly with appropriate FDA personnel on a priority basis. Please contact me at 802-527-7792 if any questions or need for discussion arises.

Sincerely,

W.E. Brochu, Ph.D.
Vice President Regulatory Affairs and Quality

RECEIVED
APR 0 7 2003
OGD / CDER

MYLAN TECHNOLOGIES INC.

ORIG AMENDMENT
N/AB

Mr. Gary Buehler
Director, Office of Generic Drugs
CDER (HFD600)
Food and Drug Administration
Metro Park North II
Room 150
7500 Standish Place
Rockville MD 20855-2773

MINOR Amendment – Drug Release

ANDA 76-258
Fentanyl Transdermal Systems
25, 50, 75 and 100mcg/hr

DATE DEC 20 2002

Dear Mr. Buehler:

Reference is made to ANDA 76-~~268~~ 258 and to the Agency's comment letter of 11/22/02 (Bioequivalency Amendment).

Mylan hereby amends ANDA 76-~~268~~ 258 in response to the Agency's comment letter of 11/22/02.

We certify that a true copy of this amendment, as submitted to the Office of Generic Drugs, has been forwarded to FDA's New England District Office.

This amendment is submitted in duplicate. Should you require additional information or have any questions regarding this amendment, please contact the undersigned at 802-527-7792, ext 426 or via facsimile 802-527-8155.

Sincerely,

W.E. Brochu, Ph.D.
Vice President, Regulatory & Quality Affairs

RECEIVED
DEC 23 2002
OGD / CDER

MYLAN TECHNOLOGIES INC.

Mr. Gary Buehler
Director, Office of Generic Drugs
CDER (HFD600)
Food and Drug Administration
Metro Park North II
Room 150
7500 Standish Place
Rockville MD 20855-2773

MINOR Amendment –
Chemistry, Manufacturing & Controls

ANDA 76-258
Fentanyl Transdermal Systems
25, 50, 75 and 100mcg/hr

N/AM

DATE NOV 20 2002

Dear Mr. Buehler:

Reference is made to ANDA 76-268 and to the Agency's comment letter of 11/05/02 (CMC).

Mylan hereby submits full responses to the Agency's comment letter of 11/05/02. A copy of this comment letter has been included for the reviewer's convenience.

We certify that a true copy of this amendment, as submitted to the Office of Generic Drugs, has been forwarded to FDA's New England District Office.

This amendment is submitted in duplicate. Should you require additional information or have any questions regarding this amendment, please contact the undersigned at 802-527-7792, ext 426 or via facsimile 802-527-8155.

Sincerely,

W.E. Brochu, Ph.D.
Vice President, Regulatory & Quality Affairs

RECEIVED
NOV 21 2002
OGD / CDER

11-27-02

MYLAN TECHNOLOGIES INC.

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs
CDER (HFD600)
Food and Drug Administration
Metro Park North II
7500 Standish Place
Rockville MD 20855-2773

ANDA# 76-258

Fentanyl Transdermal System 25mcg/hr, 50mcg/hr, 75mcg/hr, and 100mcg/hr

BIOAVAILABILITY

Bioequivalency Amendment

ORIG AMENDMENT

DATE OCT 14 2002

N/AB

Dear Dr. Conner:

Reference is made to Mylan's ANDA#76-258, to the Agency's Bioequivalence Comment letter of 4/18/02, to Mylan's Controlled Correspondence (Request for Reconsideration) dated 5/13/02, and to a telephone discussion on 10/8/02 with the Bioequivalence Project Manager, Ms Nina Nwaba.

Mylan hereby amends its application to provide complete responses to comments 2 through 5 of the Agency letter of 4/18/02. This amendment is submitted in duplicate.

Ms Nwaba advised that the Agency's review of the need for additional sensitization data (comment #1 of the Agency's letter of 4/18/02) is being addressed as a separate matter by the Medical Officer in the Office of Generic Drugs. On this basis she advised that Mylan's responses to the remainder of the Agency's comment letter may be submitted for review at this time.

Should you require additional information of have any questions regarding this amendment, please contact the undersigned at 802-527-7792, ext. 426 or via facsimile (802-527-8155).

Sincerely,

W.E. Brochu, Ph.D.
Vice President, Regulatory and Quality Affairs

RECEIVED
OCT 15 2002
OGD / CDER

Fentanyl Transdermal System, 25 mcg/hr

Mylan Technologies, Inc.
Attention: W.E. Brochu, Ph.D.
110 Lake Street
St. Albans, VT 05478

Reference Number: P02-026
OGD# 02-369
ANDA 76-258

Dear Dr. Brochu:

Reference is made to the proposed bioequivalence study protocols and correspondence dated May 6, May 13, and June 21, 2002, submitted to the Office of Generic Drugs (OGD) for review, regarding skin irritation and sensitization studies for Fentanyl Transdermal System, 25 mcg/hr:

The protocols have been reviewed by the Division of Bioequivalence (DBE), and we have the following comments for your consideration:

1. Your proposed protocols FENT-0249 and FENT-0252 are not acceptable. FENT-0252 cannot be considered sufficiently safe to proceed, and the rotating patch design in FENT-0249 is inadequate as a provocative irritation and sensitization study.

2. No further studies of dermal irritation and sensitization or patch adhesion are required for your proposed fentanyl transdermal system. The data from FENT-0134 demonstrate that repeated same-site applications of the 25 mcg/hr dose can result in dangerously high serum fentanyl concentrations, making it unsafe to conduct the provocative studies that would otherwise be needed. The small number of subjects and open design with between-subject comparison do not provide any meaningful comparison of dermal reactions between your product and Duragesic®. However, studies FENT-0132 and FENT-0133, along with your literature overview of dermatological reactions produced by transdermal fentanyl, are adequate to demonstrate that use of your Fentanyl Transdermal System is unlikely to result in a degree of skin irritation or sensitization that is greater than that seen with use of the reference product Duragesic® Transdermal System.

The guidance offered in this correspondence represents the best judgement the Office can offer based on the submitted information, current scientific knowledge, and the proposed issue (s) at hand. Revisions of our statements may be necessary as needed. Should you have any questions, please call Steven Mazzella, R.Ph., at (301) 827-5847. In future correspondence regarding this issue, please include a copy of this letter.

Sincerely yours,

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

CC:

HFD-650
File P02-026
OGD 02-369

Bio Protocol Letter

Endorsements:

Dena Hixon, M.D.
Associate Director for Medical Affairs
Office of Generic Drugs

APPEARS THIS WAY
ON ORIGINAL

Dale Conner/HFD-650 10/10/02
Lizzie Sanchez/HFD-650
Steven Mazzella/HFD-650

Revisions:

Lizzie Sanchez/ (ALS\10/7/02)

Drafted by S. Mazzella\10/7/02
V:\firmsam\mylan\ltrs&rev\P02-026

4.1

MYLAN TECHNOLOGIES INC.

AUG – 7 2002

Mr. Gary Buehler
Director, Office of Generic Drugs
CDER (HFD600)
Food and Drug Administration
Metro Park North II
Room 150
7500 Standish Place
Rockville MD 20855-2773

MINOR AMENDMENT
LABELING

ORIG AMENDMENT
N/AM

ANDA 76-258

FENTANYL TRANSDERMAL SYSTEM,
25mcg/hr, 50mcg/hr, 75mcg/hr, and 100mcg/hr

Dear Mr. Buehler:

Reference is made to the pending application identified above and to telephone correspondence with the Agency on 7/19/02 and 7/23/02. Copies of the contact reports are provided.

This amendment provides revised prescribing information for Fentanyl Transdermal System. This labeling was revised in response to the July conversations with the Agency referenced above, in which Mylan was asked to remove the word ' ——— from two sections of this labeling: 1) the Precautions/Cardiac Disease section and 2) the Pharmacodynamics/ Cardiovascular Effects section. The word ' ——— has been removed from these two sections. These are the only changes being made.

We are submitting one (1) complete copy of this finished product labeling (FPL) with the archival copy of this amendment and twelve (12) copies are attached to the review copy. In addition, Mylan has provided a side by side comparison of Mylan's previously submitted labeling and Mylan's revised labeling.

Should you require additional information or have any questions regarding this amendment, please contact the undersigned at (802) 527-7792, ext. 426 or via facsimile (802) 527-8155.

Sincerely,

W.E. Brochu, Ph.D.
Vice President, Regulatory Affairs and Quality

RECEIVED
AUG 0 8 2002
OGD / CDER

4.1

MYLAN TECHNOLOGIES INC.

ORIG AMENDMENT
N/AM

Dr. Gary Buehler
Director, Office of Generic Drugs
CDER (HFD600)
Food and Drug Administration
Metro Park North II
Room 150
7500 Standish Place
Rockville MD 20855-2773

ANDA # 76-258

Fentanyl Transdermal System, 25µg/hr, 50µg/hr, 75µg/hr, and 100µg/hr

Minor Amendment (CMC)- Raw Material Specification Change
Date: JUL 3 1 2002

Dear Dr. Buehler:

Reference is made of our ANDA 76-258 for Fentanyl Transdermal Systems 25µg/hr, 50µg/hr, 75µg/hr, and 100µg/hr and to Minor Amendment (CMC and labeling) dated June 20, 2002.

The raw material specification for Fentanyl _____ that was submitted in our minor amendment dated June 20, 2002 contained an error in the appearance specification.

On March 19th of 2002, our vendor for this raw material made a change to the appearance specification of this material in order to comply with the European Pharmacopoeia. The appearance specification at this time was changed from ' _____ to _____

This change in the appearance specification was inadvertently not included in Mylan's minor amendment made on June 20, 2002.

Please advise if there are any questions related to this amendment.

Sincerely,

W.E. Brochu, Ph.D.
Vice President, Regulatory Affairs and Quality

RECEIVED
AUG 0 1 2002
OGD / CDER

MYLAN TECHNOLOGIES INC.

JUN 20 2002

Mr. Gary Buehler
Director, Office of Generic Drugs
CDER (HFD600)
Food and Drug Administration
Metro Park North II
Room 150
7500 Standish Place
Rockville MD 20855-2773

ORIG AMENDMENT
N/AM

FPL

MINOR AMENDMENT
CMC and LABELING

ANDA 76-258

FENTANYL TRANSDERMAL SYSTEM,
25mcg/hr, 50mcg/hr, 75mcg/hr, and 100mcg/hr

Dear Mr. Buehler:

Reference is made to the pending application identified above and to the Agency's comment letter dated 4/15/02 pertaining to this application. A copy of the Agency correspondence is attached for the reviewer's convenience.

This amendment provides complete responses to the Agency's CMC and Labeling comments. We have additionally amended our finished product specification to include a test and limit for _____ The test method, method validation summary report and revised finished product specification are included in this amendment. Finally, we are submitting final printed labeling (FPL); one (1) complete copy of the FPL is attached to the archival copy and twelve (12) copies are attached to the review copy of this submission.

We certify that a true copy of the CMC elements of this amendment, as submitted to the Office of Generic Drugs, has been forwarded to the FDA's New England District Office.

This amendment is submitted in duplicate. Should you require additional information or have any questions regarding this amendment, please contact the undersigned at (802) 527-7792, ext. 426 or via facsimile (802) 527-8155.

Sincerely,

Wm E. Brochu

W.E. Brochu, Ph.D.
Vice President, Regulatory Affairs and Quality

RECEIVED
JUN 21 2002
OGD / CDER

MYLAN TECHNOLOGIES INC.

NAF
MHS 6-19-02
Alza v Jansen initiated suit on day
No :- No 30 month stay

NEW CORRESP

NC

June 11, 2002

Office of Generic Drugs, CDER, FDA
Mr. Gary Buehler, Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: Fentanyl Transdermal System, 25 µg/hr, 50µg/hr, 75µg/hr, and 100µg/hr
ANDA NO. 76-258
PATENT AMENDMENT

Dear Mr. Buehler:

This amendment is in response to Mr. Martin Shimer's June 10, 2002 voice-mail message to Mr. William Brochu requesting that Mylan Technologies, Inc. ("Mylan") submit a patent amendment providing documentation that it was not sued by the patent owner/NDA holder for the subject reference listed drug product, Duragesic Transdermal Systems within the 45-day period after notice was received from Mylan.

Mylan has previously submitted a copy of the return receipt request signed by a representative of the owner of the patent/NDA holder, both of whom are the same. As indicated in a previous amendment, the owner of the patent/NDA holder initiated suit against Mylan on January 25, 2002. Enclosed as you requested is a copy of the appropriate court document (face sheet from Complaint) that identifies the date upon which Mylan was sued by the patent owner/NDA holder, Alza Corporation.

This documentation clearly indicates that suit was initiated by the owner of the patent/NDA holder after the allowable 45-day period as identified in 21 CFR 314.95(f). For this reason Mylan believes that it is entitled to immediate effective approval of its ANDA once the regulatory requirements are satisfied.

Sincerely,

W.E. Brochu, Ph.D
Vice President, Regulatory Affairs and Quality

RECEIVED
JUN 12 2002
OGD / CDER

MYLAN TECHNOLOGIES INC.

FEB 5 2002

NAF Mail B See note on next page NEW CORRESP

Dr. Gary Buehler
Director, Office of Generic Drugs
CDER (HFD600)
Food and Drug Administration
Metro Park North II
Room 150
7500 Standish Place
Rockville MD 20855-2773

ANDA # 76-258

Fentanyl Transdermal System, 25μg/hr, 50μg/hr, 75μg/hr, and 100μg/hr

Patent Amendment

Dear Dr. Buehler:

Reference is made of our ANDA 76-258 for Fentanyl Transdermal Systems 25μg/hr, 50μg/hr, 75μg/hr, and 100μg/hr. Enclosed please find a patent amendment as required by 21 CFR 314.95(e).

Please advise if there are any questions related to this amendment.

Sincerely,

William E. Brochu Jr

W.E. Brochu, Ph.D.
Vice President, Regulatory Affairs and Quality

CENTER FOR DRUG EVALUATION AND RESEARCH
FEB 06 2002
OGD

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MYLAN TECHNOLOGIES INC.

NFI
MHB 6-10-02
Mandy called & asked that Mylan Tech submit a Patent Amendment that confirms initiation of litigation by Alza AS 1/25/02 & also provides the C.A.# Action #.

February 5, 2002

Office of Generic Drugs, CDER, FDA
Mr. Gary Buehler, Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: Fentanyl Transdermal System, 25 µg/hr, 50µg/hr, 75µg/hr, and 100µg/hr
ANDA NO. 76-258
PATENT AMENDMENT

Dear Mr. Buehler:

Pursuant to 21 CFR 314.95(e), Mylan hereby amends the above referenced application with documentation of receipt of the notice required by 21 CFR 314.95(a). Said notice met the content requirements under 21 C.F.R. 314.95(c). The owner of the patent, and the holder of the application for the listed drug claimed by said patent was served with the required notice referenced above. Notice was served on Alza Corporation ("Alza") and proof of delivery by Registered Mail, Return Receipt evidences receipt by Alza on December 10, 2001. A copy of the documentation evidencing Mylan's service and receipt by Alza is enclosed.

With respect to the above-referenced product, Mylan received notice that Alza commenced litigation against Mylan on January 25, 2002 which was after the forty-five (45) day statutory period had expired Therefore, Mylan will market its Fentanyl Transdermal System, 25 µg/hr, 50µg/hr, 75µg/hr, and 100µg/hr after all regulatory requirements have been met and FDA has completed its review of this application.

CENTER FOR DRUG EVALUATION AND RESEARCH
FEB 06 2002

Sincerely,

William E. Brochu

W.E. Brochu, Ph.D
Vice President, Regulatory Affairs and Quality

MYLAN TECHNOLOGIES INC.

January 31, 2002

Office of Generic Drugs, CDER, FDA
Gary J. Buehler, Acting Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

NEW CORRESP

NC BIO

RE: FENTANYL TRANSDERMAL SYSTEM, 25 µg/hr

BIOEQUIVALENCE ELECTRONIC AMENDMENT ESD

Dear Mr. Buehler:

Reference is made to the Abbreviated New Drug Application (ANDA 76-258) for the referenced product that was submitted to the Agency on October 12, 2001 and to our electronic submission made on December 21, 2001. Please find enclosed a diskette providing an amendment to our electronic submission. This amendment provides frozen plasma stability data for the Fentanyl assay. A copy of Mylan's declaration that the data contained on the electronic bioequivalence diskette is identical to the paper submission except as noted in the companion document is presented in Attachment 1.

Reference is also made to amendment dated 12/4/01, which was made to ANDA 76-258 in order to include three additional Fentanyl Transdermal System product strengths (50µg/hr, 75µg/hr, and 100µg/hr). In a conversation earlier today (1/31/02), I was advised by Ms. Ruth Warzala at FDA (EVA) that it would not be necessary to include the electronic data for these three strengths since a bio waiver has been requested. For this reason we have not submitted an electronic amendment for the additional Fentanyl Transdermal System product strengths.

Should you have any questions or require additional information, please contact the undersigned at telephone number (802) 527-7792, extension 426 and/or facsimile number (802) 527-8155.

Sincerely,

Willam E. Brochu, Ph.D.
Vice President Regulatory Affairs and Quality

Enclosures

CENTER FOR DRUG EVALUATION AND RESEARCH
FEB 01 2002

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MYLAN TECHNOLOGIES INC.

December 21, 2001

Office of Generic Drugs, CDER, FDA
Gary J. Buehler, Acting Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

NC

RE: FENTANYL TRANSDERMAL SYSTEM, 25 µg/hr

BIOEQUIVALENCE ELECTRONIC SUBMISSION ESD

Dear Mr. Buehler:

Reference is made to the Abbreviated New Drug Application (ANDA 76-258) for the referenced product that was submitted to the Agency on October 12, 2001. Please find enclosed is a diskette providing the electronic submission, ESD, for the bioequivalence studies that were submitted in the ANDA. A copy of Mylan's declaration that the data contained on the electronic bioequivalence diskette is identical to the paper submission except as noted in the companion document is presented in Attachment 1.

Should you have any questions or require additional information, please contact the undersigned at telephone number (802) 527-7792, extension 429 and/or facsimile number (802) 527-8155.

Sincerely,

Willam E. Brochu, Ph.D.
Vice President Regulatory Affairs and Quality

Enclosures

CENTER FOR DRUG EVALUATION AND RESEARCH
DEC 26 2001
OGD

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MYLAN TECHNOLOGIES INC.

DEC 4 2001

ANDA # 76-258

Dr. Gary Buehler
Director, Office of Generic Drugs
CDER (HFD600)
Food and Drug Administration
Metro Park North II
Room 150
7500 Standish Place
Rockville MD 20855-2773

Fentanyl Transdermal System, 25 µg/hr

Major Amendment

50µg/hr, 75µg/hr, and 100µg/hr strengths

Bioequivalence Waiver Request

505(b)(2)DOC
16-JAN-2002

ORIG AMENDMENT
N/A C

Dear Dr. Buehler:

Reference is made to MYLAN TECHNOLOGIES, INC.'s ANDA # 76-258 for Fentanyl Transdermal System, 25µg/hr dated October 12, 2001. This amendment provides the addition of 50µg/h, 75µg/hr, and 100µg/hr as additional product strengths.

This amendment to our application provides for the manufacture of the additional strengths of the transdermal system, 50µg/hr, 75µg/hr, and 100µg/hr. These product strengths correspond to the reference listed products Duragesic® 50µg/hr, 75µg/hr and 100µg/hr respectively. A waiver of the in-vivo bioequivalence data requirement is requested on the basis of our demonstration of bioequivalence of our 25µg/hr product with Duragesic® filed in our original application. These additional product strengths are prepared from similar [redacted] and differ from the 25µg/hr strength originally submitted in product (patch) area only.

We are also revising the patent certification originally included in our submission to include the 50µg/hr, 75µg/hr, and 100µg/hr product strengths provided in this amendment. The patent holders will be notified of this amendment as required by regulations.

This amendment also provides a revised specification for the finished product. The finished product specification has been revised since the original submission in order to include a second test for identification (test B). The specification for all four product strengths contains the second test for identification. The revised test method for identification (STM-0484) and the corresponding revised method validation report are also provided.

Also provided in this amendment are two revised method validation reports. The first (STM-0482, Related Compounds in Fentanyl [redacted]) was revised in order to correct a calculation error in the accuracy parameter and the second (STM-0487, Related Compounds in Fentanyl Transdermal System) was revised in order to correct a typographical error on page 1 and to update the selectivity data.

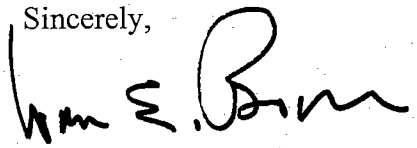
CDER OFFICIAL DOCUMENT
DEC 05 2001
OGD
EVALUATION AND RESEARCH

As required by 21 CFR 314 (d)(5), we certify that a true copy of the technical sections of this amendment, as submitted to the Office of Generic Drugs, has been forwarded to the FDA New England District Office.

Two copies, an archival and review copy, of this submission are provided. The amendment is organized by sections recommended for the format and content of an ANDA. We have not resubmitted information that is not changed by this amendment. To assist the reviewer, we have included references to our original submission October 12, 2001 in appropriate sections where unchanged documents that apply to all 4 strengths were included in our original submission, such as specifications for the API and inactive ingredients.

All correspondence concerning this application should be directed to the attention of the undersigned at MYLAN TECHNOLOGIES, INC., 110 Lake Street, St. Albans, VT 05478 (FAX: (802) 527-8155, phone: (802) 527-7792 – ext. 426).

Sincerely,



W.E. Brochu, Ph.D.
Vice President Regulatory Affairs and Quality

APPEARS THIS WAY
ON ORIGINAL

ANDA 76-258

NOV 26

Mylan Technologies, Inc.
Attention: W.E. Brochu, Ph.D.
110 Lake Street
St. Albans, VT 05478

Dear Sir:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

NAME OF DRUG: Fentanyl Transdermal Extended-release Film, 0.6 mg/day

DATE OF APPLICATION: October 12, 2001

DATE (RECEIVED) ACCEPTABLE FOR FILING: October 15, 2001

You have filed a Paragraph IV patent certification, in accordance with 21 CFR 314.94(a)(12)(i)(A)(4) and Section 505(j)(2)(A)(vii)(IV) of the Act. Please be aware that you need to comply with the notice requirements, as outlined below. In order to facilitate review of this application, we suggest that you follow the outlined procedures below:

CONTENTS OF THE NOTICE

You must cite section 505(j)(2)(B)(ii) of the Act in the notice and should include, but not be limited to, the information as described in 21 CFR 314.95(c).

SENDING THE NOTICE

In accordance with 21 CFR 314.95(a):

- Send notice by U.S. registered or certified mail with return receipt requested to each of the following:

  1) Each owner of the patent or the representative designated by the owner to receive the notice;
  2) The holder of the approved application under section 505(b) of the Act for the listed drug claimed by the patent and for which the applicant is seeking approval.

3) An applicant may rely on another form of documentation only if FDA has agreed to such documentation in advance.

DOCUMENTATION OF NOTIFICATION/RECEIPT OF NOTICE

You must submit an amendment to this application with the following:

- In accordance with 21 CFR 314.95(b), provide a statement certifying that the notice has been provided to each person identified under 314.95(a) and that notice met the content requirements under 314.95(c).

- In accordance with 21 CFR 314.95(e), provide documentation of receipt of notice by providing a copy of the return receipt or a letter acknowledging receipt by each person provided the notice.

- A designation on the exterior of the envelope and above the body of the cover letter should clearly state "PATENT AMENDMENT". This amendment should be submitted to your application as soon as documentation of receipt by the patent owner and patent holder is received.

DOCUMENTATION OF LITIGATION/SETTLEMENT OUTCOME

You are requested to submit an amendment to this application that is plainly marked on the cover sheet "PATENT AMENDMENT" with the following:

- If litigation occurs within the 45-day period as provided for in section 505(j)(4)(B)(iii) of the Act, we ask that you provide a copy of the pertinent notification.

- Although 21 CFR 314.95(f) states that the FDA will presume the notice to be complete and sufficient, we ask that if you are not sued within the 45-day period, that you provide a letter immediately after the 45 day period elapses, stating that no legal action was taken by each person provided notice.

- You must submit a copy of a court order or judgement or a settlement agreement between the parties, whichever is applicable, or a licensing agreement between you and the patent holder, or any other relevant information. We ask that this information be submitted promptly to the application.

If you have further questions you may contact Gregg Davis, Chief, Regulatory Support Branch, at (301) 827-5862.

We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

Jeen Min
Project Manager
(301) 827-5849

Sincerely yours,

Gregory S. Davis for

Wm Peter Rickman
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 76-258
DUP/Jacket
Division File
Field Copy
HFD-610/R.West
HFD-610/P.Rickman
HFD-92
HFD-615/M.Bennett
HFD-600/

Endorsement: HFD-615/GDavis, Chief, RSB Davis 26-NOV-2001 date
HFD-615/SMiddleton, CSO S. Middleton date 11/26/01
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FT/StM 11/26/01
ANDA Acknowledgment Letter!