FENTANYL TRANSDERMAL- fentanyl transdermal patch, extended release
SpecGx LLC

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use FENTANYL TRANSDERMAL SYSTEM safely and effectively. See full prescribing information for FENTANYL TRANSDERMAL SYSTEM.

FENTANYL transdermal system, CII

Initial U.S. Approval: 1968

WARNING: SERIOUS AND LIFE-THREATENING RISKS FROM USE OF FENTANYL TRANSDERMAL SYSTEM

See full prescribing information for complete boxed warning.

- **Fentanyl transdermal system exposes users to risks of addiction, abuse, and misuse, which can lead to overdose and death. Assess patient's risk before prescribing and reassess regularly for these behaviors or conditions. (5.1)**
- **Serious, life-threatening, or fatal respiratory depression may occur, especially upon initiation or following a dosage increase. To reduce the risk of respiratory depression, proper dosing and titration of fentanyl transdermal system are essential. (5.2)**
- **Accidental exposure to fentanyl transdermal system, especially in children, can result in fatal overdose of fentanyl. (5.3)**
- **Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death. Reserve concomitant prescribing for use in patients for whom alternative treatment options are inadequate. (5.4, 7)**
- **Advise pregnant women using opioids for an extended period of time of the risk of Neonatal Opioid Withdrawal Syndrome, which may be life-threatening if not recognized and treated. Ensure that management by neonatology experts will be available at delivery. (5.5)**
- **Healthcare providers are strongly encouraged to complete a REMS compliant education program and to counsel patients and caregivers on serious risks, safe use, and the importance of reading the Medication Guide with each prescription. (5.6)**
- **Concomitant use with CYP3A4 inhibitors (or discontinuation of CYP3A4 inducers) can result in a fatal overdose of fentanyl. (5.7)**
- **Exposure of the fentanyl transdermal system application site and surrounding area to direct external heat sources has resulted in fatal overdose of fentanyl. Warn patients to avoid exposing the fentanyl transdermal system application site and surrounding area to direct external heat sources. (5.8)**

RECENT MAJOR CHANGES

Boxed Warning	12/2025
Indications and Usage (1)	12/2025
Dosage and Administration (2.1, 2.2, 2.3, 2.9)	12/2025
Warnings and Precautions (5.1, 5.2, 5.4, 5.19, 5.21)	12/2025

INDICATIONS AND USAGE

Fentanyl transdermal system contains fentanyl, an opioid agonist, and is indicated for the management of severe and persistent pain in opioid-tolerant patients that requires an opioid analgesic and that cannot be adequately treated with alternative options, including immediate-release opioids. (1)
Patients considered opioid-tolerant are those taking, for one week or longer, at least 60 mg oral morphine

per day, 25 mcg transdermal fentanyl per hour, 30 mg oral oxycodone per day, 8 mg oral hydromorphone per day, 25 mg oral oxymorphone per day, 60 mg oral hydrocodone per day, or an equianalgesic dose of another opioid. (2.1)

Limitations of Use:

- Because of the risks of addiction, abuse, misuse, overdose, and death, which can occur at any dosage or duration and persist over the course of therapy reserve opioid analgesics, including fentanyl transdermal system, for use in patients for whom alternative treatment options are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain. (1, 5.1)
- Fentanyl transdermal system is not indicated as an as-needed (prn) analgesic. (1)

DOSAGE AND ADMINISTRATION

- Fentanyl transdermal system should be prescribed only by healthcare providers who are knowledgeable about the use of extended-release/long-acting opioids and how to mitigate the associated risks. (2.1)
- Use the lowest effective dosage for the shortest duration of time consistent with individual patient treatment goals. Reserve titration to higher doses of fentanyl transdermal system for patients in whom lower doses are insufficiently effective and in whom the expected benefits of using a higher dose opioid clearly outweigh the substantial risks. (2.1, 5)
- Initiate the dosing regimen for each patient individually, taking into account the patient's underlying cause and severity of pain, prior analgesic treatment and response, and risk factors for addiction, abuse, and misuse. (5.1)
- Respiratory depression can occur at any time during opioid therapy, especially when initiating and following dosage increases with fentanyl transdermal system. Consider this risk when selecting an initial dose and when making dose adjustments. (2.1, 5.2)
- Discuss opioid overdose reversal agents and options for acquiring them with the patient and/or caregiver, both when initiating and renewing treatment with fentanyl transdermal system, especially if the patient has additional risk factors for overdose, or close contacts at risk for exposure and overdose. (2.2, 5.1, 5.2, 5.4)
- Initial dose selection: consult conversion instructions. (2.3)
- Periodically reassess patients receiving fentanyl transdermal system to evaluate the continued need for opioid analgesics to maintain pain control, for the signs or symptoms of adverse reactions, and for the development of addiction, abuse, or misuse. (2.4)
- Each transdermal system is intended to be worn continuously for up to 72 hours. (2.3, 2.7)
- Adhere to instructions concerning administration and disposal of fentanyl transdermal system. (2.7, 2.8)
- Mild to moderate hepatic and renal impairment: Initiate treatment with one-half the usual starting dose, titrate slowly, and regularly evaluate for signs of respiratory and central nervous system depression. (2.5, 2.6)
- Do not rapidly reduce or abruptly discontinue fentanyl transdermal system in a physically-dependent patient because rapid reduction or abrupt discontinuation of opioid analgesics has resulted in serious withdrawal symptoms, uncontrolled pain, and suicide. (2.9, 5.21)

DOSAGE FORMS AND STRENGTHS

Transdermal System: 12 mcg/hour, 25 mcg/hour, 37.5 mcg/hour, 50 mcg/hour, 62.5 mcg/hour, 75 mcg/hour, 100 mcg/hour. (3)

CONTRAINDICATIONS

- Opioid non-tolerant patients. (4)
- Acute or intermittent pain, postoperative pain, mild pain. (4)
- Significant respiratory depression. (4)
- Acute or severe bronchial asthma in an unmonitored setting or in absence of resuscitative equipment. (4)
- Known or suspected gastrointestinal obstruction, including paralytic ileus. (4)
- Known hypersensitivity to fentanyl or any of the components of the transdermal system. (4)

WARNINGS AND PRECAUTIONS

- Risk of Increased Fentanyl Absorption with Elevated Body Temperature: Regularly evaluate patients with fever closely for sedation and respiratory depression and reduce the dose if necessary. Warn patients to avoid strenuous exertion that may lead to increased body temperature. (5.9)
- Opioid-Induced Hyperalgesia (OIH) and Allodynia: Opioid-Induced Hyperalgesia (OIH) occurs when an opioid analgesic paradoxically causes an increase in pain, or an increase in sensitivity to pain. If OIH is suspected, carefully consider appropriately decreasing the dose of the current opioid analgesic or opioid rotation. (5.10)
- Serotonin Syndrome with Concomitant Use of Serotonergic Drugs: Potentially life-threatening condition

could result from concomitant serotonergic drug administration. Discontinue fentanyl transdermal system immediately if serotonin syndrome is suspected. (5.11)
- Life-Threatening Respiratory Depression in Patients with Chronic Pulmonary Disease or in Elderly, Cachectic, or Debilitated Patients: Regularly evaluate, particularly during initiation and titration. (5.12)
- Adrenal Insufficiency: If diagnosed, treat with physiologic replacement of corticosteroids, and wean patient off of the opioid. (5.13)
- Severe Hypotension: Regularly evaluate during dose initiation and titration. Avoid the use of fentanyl transdermal system in patients with circulatory shock. (5.14)
- Risks of Use in Patients with Increased Intracranial Pressure, Brain Tumors, Head Injury or Impaired Consciousness: Monitor for sedation and respiratory depression. Avoid use of fentanyl transdermal system in patients with impaired consciousness or coma. (5.15)

ADVERSE REACTIONS

Most common adverse reactions (≥5%) are nausea, vomiting, somnolence, dizziness, insomnia, constipation, hyperhidrosis, fatigue, feeling cold, anorexia, headache, and diarrhea. (6)
To report SUSPECTED ADVERSE REACTIONS, contact Mallinckrodt at 1-800-778-7898 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

Mixed Agonist/Antagonist and Partial Agonist Opioid Analgesics: Avoid use with fentanyl transdermal system because they may reduce analgesic effect of fentanyl transdermal system or precipitate withdrawal symptoms. (5.21, 7)

USE IN SPECIFIC POPULATIONS

- Pregnancy: May cause fetal harm. (8.1)
- Lactation: Not recommended. (8.2)
- Severe Hepatic and Renal Impairment: Use not recommended. (8.6, 8.7)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 4/2026

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FULL PRESCRIBING INFORMATION

WARNING: SERIOUS AND LIFE-THREATENING RISKS FROM USE OF FENTANYL TRANSDERMAL SYSTEM

Addiction, Abuse, and Misuse

Because the use of fentanyl transdermal system exposes patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death, assess each patient's risk prior to prescribing and reassess all patients regularly for the development of these behaviors and conditions *[see Warnings and Precautions (5.1)]*.

Life-Threatening Respiratory Depression

Serious, life-threatening, or fatal respiratory depression may occur with use of fentanyl transdermal system, especially during initiation or following a dosage increase. To reduce the risk of respiratory depression, proper dosing and titration of fentanyl transdermal system are essential *[see Warnings and Precautions (5.2)].*

Accidental Exposure

Accidental exposure of even one dose of fentanyl transdermal system, especially in children, can result in a fatal overdose of fentanyl *[see Warnings and Precautions (5.3)]*. Deaths due to an overdose of fentanyl have occurred when children and adults were accidentally exposed to fentanyl transdermal system. Strict adherence to the recommended handling and disposal instructions is of the utmost importance to prevent accidental exposure *[see Warnings and Precautions (5.3)]*.

Risks From Concomitant Use With Benzodiazepines Or Other CNS Depressants

Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death. Reserve concomitant prescribing of fentanyl transdermal system and benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are inadequate *[see Warnings and Precautions (5.4), Drug Interactions (7)]*.

Neonatal Opioid Withdrawal Syndrome (NOWS)

Advise pregnant women using opioids for an extended period of time of the risk of Neonatal Opioid Withdrawal Syndrome, which may be life-threatening if not recognized and treated. Ensure that management by neonatology experts will be available at delivery *[see Warnings and Precautions (5.5)]*.

Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS)

Healthcare providers are strongly encouraged to complete a REMS-compliant education program and to counsel patients and caregivers on serious risks, safe use, and the importance of reading the Medication Guide with each prescription *[see Warnings and Precautions (5.6)].*

Cytochrome P450 3A4 Interaction

The concomitant use of fentanyl transdermal system with all cytochrome P450 3A4 inhibitors may result in an increase in fentanyl

plasma concentrations, which could increase or prolong adverse drug effects and may cause potentially fatal respiratory depression. In addition, discontinuation of a concomitantly used cytochrome P450 3A4 inducer may result in an increase in fentanyl plasma concentration. Monitor patients receiving fentanyl transdermal system and any CYP 3A4 inhibitor or inducer *[see Warnings and Precautions (5.7), Clinical Pharmacology (12.3)].*

Risk of Increased Fentanyl Absorption with Application of External Heat
Exposure of the fentanyl transdermal system application site and surrounding area to direct external heat sources, such as heating pads or electric blankets, heat or tanning lamps, sunbathing, hot baths, saunas, hot tubs, and heated water beds may increase fentanyl absorption and has resulted in fatal overdose of fentanyl. Warn patients to avoid exposing the application site and surrounding area to direct external heat sources *[see Warnings and Precautions (5.8)].*

1 INDICATIONS AND USAGE

Fentanyl transdermal system is indicated for the management of severe and persistent pain in opioid-tolerant patients that requires an opioid analgesic and that cannot be adequately treated with alternative options, including immediate-release opioids.

Patients considered opioid-tolerant are those who are taking, for one week or longer, at least 60 mg morphine per day, 25 mcg transdermal fentanyl per hour, 30 mg oral oxycodone per day, 8 mg oral hydromorphone per day, 25 mg oral oxymorphone per day, 60 mg oral hydrocodone per day, or an equianalgesic dose of another opioid.

Limitations of Use

- Because of the risks of addiction, abuse, misuse, overdose, and death, which can occur at any dosage or duration and persist over the course of therapy *[see Warnings and Precautions (5.1)]*, reserve opioid analgesics, including fentanyl transdermal system, for use in patients for whom alternative treatment options are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain.
- Fentanyl transdermal system is not indicated as an as-needed (prn) analgesic.

2 DOSAGE AND ADMINISTRATION

2.1 Important Dosage and Administration Instructions

- Fentanyl transdermal system should be prescribed only by healthcare professionals who are knowledgeable about the use of extended-release/long-acting opioids and how to mitigate the associated risks.
- Due to the risk of respiratory depression, fentanyl transdermal system is only indicated for use in patients who are already opioid-tolerant. Discontinue or taper all other extended-release opioids when beginning fentanyl transdermal system therapy. As fentanyl transdermal system is only for use in opioid-tolerant patients, do not begin any patient on fentanyl transdermal system as the first opioid *[see Indications and Usage (1)]*.

- Use the lowest effective dosage for the shortest duration of time consistent with individual patient treatment goals *[see Warnings and Precautions (5)]*. Because the risk of overdose increases as opioid doses increase, reserve titration to higher doses of fentanyl transdermal system for patients in whom lower doses are insufficiently effective and in whom the expected benefits of using a higher dose opioid clearly outweigh the substantial risks.
- Initiate the dosing regimen for each patient individually, taking into account the patient's underlying cause and severity of pain, prior analgesic treatment and response, and risk factors for addiction, abuse, and misuse *[see Warnings and Precautions (5.1)]*.
- Respiratory depression can occur at any time during opioid therapy, especially when initiating and following dosage increases with fentanyl transdermal system. Consider this risk when selecting an initial dose and when making dose adjustments *[see Warnings and Precautions (5)]*.
- Each fentanyl transdermal system is worn continuously for up to 72 hours *[see Dosage and Administration (2.7)]*.

2.2 Patient Access to an Opioid Overdose Reversal Agent for the Emergency Treatment of Opioid Overdose

Inform patients and caregivers about opioid overdose reversal agents (e.g., naloxone, nalmefene). Discuss the importance of having access to an opioid overdose reversal agent, especially if the patient has risk factors for overdose (e.g., concomitant use of CNS depressants, a history of opioid use disorder, or prior opioid overdose) or if there are household members (including children) or other close contacts at risk for accidental ingestion or opioid overdose. The presence of risk factors for overdose should not prevent the management of pain in any patient *[see Warnings and Precautions (5.1, 5.2, 5.4)]*.

Discuss the options for obtaining an opioid overdose reversal agent (e.g., prescription, over-the-counter, or as part of a community-based program) *[see Warnings and Precautions (5.2)]*.

There are important differences among the opioid overdose reversal agents, such as route of administration, product strength, approved patient age range, and pharmacokinetics. Be familiar with these differences, as outlined in the approved labeling for those products, prior to recommending or prescribing such an agent.

2.3 Initial Dosage

It is safer to underestimate a patient's 24-hour fentanyl dosage and provide rescue medication (e.g., immediate-release opioid) than to overestimate the 24-hour fentanyl dosage and manage an adverse reaction due to an overdose. While useful tables of opioid equivalents are readily available, there is inter-patient variability in the potency of opioid drugs and opioid formulations. Frequently reevaluate patients for signs and symptoms of opioid withdrawal and for signs of oversedation/toxicity after converting patients to fentanyl transdermal system.

- Do not initiate treatment with fentanyl transdermal system in patients who are not opioid tolerant *[see Contraindications (4)]*.
- The recommended starting dose when converting from other opioids to fentanyl transdermal system is intended to minimize the potential for overdosing patients with the first dose.

- When fentanyl transdermal system therapy is initiated, discontinue all opioid analgesics other than those used on an as needed basis for breakthrough pain when appropriate.
- Each fentanyl transdermal system is worn continuously for up to 72 hours *[see Dosage and Administration (2.7)].*

In a fentanyl transdermal system clinical trial, patients were converted from their prior opioid to fentanyl transdermal system using **Table 1** as a guide for the initial fentanyl transdermal system dose.

When converting patients from oral or parenteral opioids to fentanyl transdermal system, use **Table 1** (alternatively use **Table 2** for adult and pediatric patients taking opioids or doses not listed in **Table 1**) and consider the following:

- These are **not** tables of equianalgesic doses.
- The conversion doses in these tables are only for the conversion **from** one of the listed oral or parenteral opioid analgesics **to** fentanyl transdermal system.
- The tables **cannot** be used to convert **from** fentanyl transdermal system **to** another opioid because these conversions will result in an overestimation of the dose of the new opioid (these conversions are conservative) and may result in fatal overdosage.

Table 1*. Dose Conversion from Other Opioids to Fentanyl Transdermal System

Current Analgesic	**Daily Dosage (mg/day)**			
Oral morphine	60-134	135-224	225-314	315-404
Intramuscular or Intravenous morphine	10-22	23-37	38-52	53-67
Oral oxycodone	30-67	67.5-112	112.5-157	157.5-202
Oral codeine	150-447			
Oral hydromorphone	8-17	17.1-28	28.1-39	39.1-51
Intravenous hydromorphone	1.5-3.4	3.5-5.6	5.7-7.9	8-10
Intramuscular meperidine	75-165	166-278	279-390	391-503
Oral methadone	20-44	45-74	75-104	105-134
Recommended Fentanyl Transdermal System Dose	25 mcg/hour	50 mcg/hour	75 mcg/hour	100 mcg/hour

* Table 1 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 1 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 (2.9)]*.

Alternatively, for adult and pediatric patients taking opioids or doses not listed in Table 1, use the following methodology when converting patients from oral or parenteral opioids to fentanyl transdermal system:

1. Calculate the previous 24-hour analgesic requirement.
2. Convert this amount to the equianalgesic oral morphine dose using a reliable reference.
3. Refer to Table 2 for 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 recommended initial fentanyl

transdermal system dose.
4. Initiate fentanyl transdermal system treatment using the recommended dose and titrate patients upwards (no more frequently than 3 days after the initial dose and every 6 days thereafter) until analgesic efficacy is attained. A 37.5 mcg/hour dose may also be used. For patients that require more than 100 mcg/hour, several transdermal systems may be used.
5. **Do not use Table 2 to convert from fentanyl transdermal system to other therapies** because this conversion to fentanyl transdermal system is conservative and will overestimate the dose of the new agent.

Table 2*. Recommended Initial Fentanyl Transdermal System Dose Based Upon Daily Oral Morphine Dose

Oral 24-hour Morphine (mg/day)	Fentanyl Transdermal System Dose (mcg/hour)
60-134	25
135-224	50
225-314	75
315-404	100
405-494	125
495-584	150
585-674	175
675-764	200
765-854	225
855-944	250
945-1034	275
1035-1124	300

* Table 2 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 2 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 (2.9)].*

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

Additional intermediate strengths 37.5 mcg/hr and 62.5 mcg/hr fentanyl transdermal systems are available and may be considered during conversion from prior opioids or dose titration. For example, the 37.5 mcg/hr system could be used before converting or titrating to a 50 mcg/hr system. Similarly a 62.5 mcg/hr system is available for use as an intermediate strength between the 50 mcg/hr and the 75 mcg/hr system.

The additional intermediate strengths, 37.5 mcg/hr and 62.5 mcg/hr, were not used in the clinical studies.

For delivery rates in excess of 100 mcg/hr, multiple systems may be used.

2.4 Titration and Maintenance of Therapy

Individually titrate fentanyl transdermal system to a dose that provides adequate analgesia and minimizes adverse reactions. Continually reevaluate patients receiving

fentanyl transdermal system to assess the maintenance of pain control, signs and symptoms of opioid withdrawal, and other adverse reactions, as well as to reassess for the development of addiction, abuse, or misuse *[see Warnings and Precautions (5.1, 5.21)]*. Frequent communication is important among the prescriber, other members of the healthcare team, the patient, and the caregiver/family during periods of changing analgesic requirements, including initial titration. During use of opioid therapy for an extended period of time, periodically reassess the continued need for opioid analgesics.

Patients who experience breakthrough pain may require a dosage adjustment of fentanyl transdermal system, or may need rescue medication with an appropriate dose of an immediate-release analgesic. If the level of pain increases after dosage stabilization, attempt to identify the source of increased pain before increasing the fentanyl transdermal system dosage.

The dosing interval for fentanyl transdermal system is 72 hours. Do not increase the fentanyl transdermal system dose for the first time until at least 3 days after the initial application. Titrate the dose based on the daily dose of supplemental opioid analgesics required by the patient on the second or third day of the initial application.

It may take up to 6 days for fentanyl levels to reach equilibrium on a new dose *[see Clinical Pharmacology (12.3)]*. Therefore, evaluate patients for further titration after no less than two 3-day applications before any further increase in dosage is made.

Base dosage increments on the daily dosage of supplementary opioids, using the ratio of 45 mg/24 hours of oral morphine to a 12 mcg/hour increase in fentanyl transdermal system dose.

If after increasing the dosage, unacceptable opioid-related adverse reactions are observed (including an increase in pain after dosage increase), consider reducing the dosage *[see Warnings and Precautions (5)]*. Adjust the dose to obtain an appropriate balance between management of pain and opioid-related adverse reactions.

A small proportion of adult patients may not achieve adequate analgesia using a 72-hour dosing interval and may require systems to be applied at 48 hours rather than at 72 hours, only if adequate pain control cannot be achieved using a 72-hour regimen. 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.

2.5 Dosage Modifications in Patients with Hepatic Impairment

Avoid the use of fentanyl transdermal system in patients with severe hepatic impairment. In patients with mild to moderate hepatic impairment, start with one-half of the usual dosage of fentanyl transdermal system. Closely monitor for signs of respiratory and central nervous system depression, including at each dosage increase *[see Warnings and Precautions (5.17), Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)]*.

2.6 Dosage Modifications in Patients with Renal Impairment

Avoid the use of fentanyl transdermal system in patients with severe renal impairment. In patients with mild to moderate renal impairment, start with one-half of the usual dosage of fentanyl transdermal system. Closely monitor for signs of respiratory and central nervous system depression, including at each dosage increase *[see Warnings and Precautions (5.18), Use in Specific Populations (8.7) and Clinical Pharmacology (12.3)]*.

2.7 Administration of Fentanyl Transdermal System

FENTANYL TRANSDERMAL SYSTEMS ARE FOR TRANSDERMAL USE ONLY.

Proper handling of fentanyl transdermal system is necessary in order to prevent serious adverse outcomes, including death, associated with accidental secondary exposure to fentanyl transdermal system *[see Warnings and Precautions (5.3)]*.

Application and Handling Instructions

- Patients should apply fentanyl transdermal system to intact, non-irritated, and non-irradiated skin on a flat surface such as the chest, back, flank, or upper arm. In young children and persons with cognitive impairment, adhesion should be monitored and the upper back is the preferred location to minimize the potential of inappropriate patch removal. Hair at the application site may be clipped (not shaved) prior to system application. If the site of fentanyl transdermal system application must be cleansed prior to application of the patch, do so with clear water. Do not use soaps, oils, lotions, alcohol, or any other agents that might irritate the skin or alter its characteristics. Allow the skin to dry completely prior to patch application.
- Patients should apply fentanyl transdermal system immediately upon removal from the sealed package. The patch must not be altered (e.g., cut) in any way prior to application. Fentanyl transdermal system should not be used if the pouch seal is broken or if the patch is cut or damaged.
- The transdermal system is 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. The next patch is applied to a different skin site after removal of the previous transdermal system.
- If problems with adhesion of the fentanyl transdermal system occur, the edges of the patch may be taped with first aid tape. If problems with adhesion persist, the patch may be overlayed with a transparent adhesive film dressing.
- If the patch falls off before 72 hours, dispose of it by folding in half and flushing down the toilet. A new patch may be applied to a different skin site.
- Patients (or caregivers who apply fentanyl transdermal system) should wash their hands immediately with soap and water after applying fentanyl transdermal system.
- Contact with unwashed or unclothed application sites can result in secondary exposure to fentanyl transdermal system and should be avoided. Examples of accidental exposure include transfer of a fentanyl transdermal system from an adult’s body to a child while hugging, sharing the same bed as the patient, accidental sitting on a patch and possible accidental exposure of a caregiver’s skin to the medication in the patch while applying or removing the patch.
- Instruct patients, family members, and caregivers to keep patches in a secure location out of the reach of children and of others for whom fentanyl transdermal

system was not prescribed.

Avoidance of Heat

Instruct patients to avoid exposing the fentanyl transdermal system application site and surrounding area to direct external heat sources, such as heating pads or electric blankets, heat or tanning lamps, sunbathing, hot baths, saunas, hot tubs, and heated waterbeds, while wearing the system *[see Warnings and Precautions (5.8)]*.

2.8 Disposal Instructions

Failure to properly dispose of fentanyl transdermal system has resulted in accidental exposures and deaths, including deaths of children *[see Warnings and Precautions (5.3)]*.

Instruct patients to dispose of used patches immediately upon removal by folding the adhesive side of the patch to itself, then flushing down the toilet.

Instruct patients to remove unused patches from their pouches, remove the protective liners, fold the patches so that the adhesive side of the patch adheres to itself, and to immediately flush the patches down the toilet.

Instruct patients to dispose of any patches remaining from a prescription as soon as they are no longer needed.

2.9 Safe Reduction or Discontinuation of Fentanyl Transdermal System

Do not rapidly reduce or abruptly discontinue fentanyl transdermal system in patients who may be physically dependent on opioids. Rapid reduction or abrupt discontinuation of opioid analgesics in patients who are physically dependent on opioids has resulted in serious withdrawal symptoms, uncontrolled pain, and suicide. Rapid reduction or abrupt discontinuation has also been associated with attempts to find other sources of opioid analgesics, which may be confused with drug-seeking for abuse. Patients may also attempt to treat their pain or withdrawal symptoms with illicit opioids, such as heroin, and other substances.

When a decision has been made to decrease the dose or discontinue therapy in an opioid-dependent patient taking fentanyl transdermal system, there are a variety of factors that should be considered, including the total daily dose of opioid (including fentanyl transdermal system) the patient has been taking, the duration of treatment, the type of pain being treated, and the physical and psychological attributes of the patient. It is important to ensure ongoing care of the patient and to agree on an appropriate tapering schedule and follow-up plan so that patient and provider goals and expectations are clear and realistic. When opioid analgesics are being discontinued due to a suspected substance use disorder, evaluate and treat the patient, or refer for evaluation and treatment of the substance use disorder. Treatment should include evidence-based approaches, such as medication assisted treatment of opioid use disorder. Complex patients with comorbid pain and substance use disorders may benefit from referral to a specialist.

There are no standard opioid tapering schedules that are suitable for all patients. Good clinical practice dictates a patient-specific plan to taper the dose of the opioid gradually.

For patients on fentanyl transdermal system who are physically opioid-dependent, initiate the taper by a small enough increment (e.g., no greater than 25% of the total daily dose) to avoid withdrawal symptoms, and proceed with dose-lowering at an interval of every 2 to 4 weeks. Patients who have been taking opioids for briefer periods of time may tolerate a more rapid taper.

It may be necessary to provide the patient with a lower dosage strength to accomplish a successful taper. Reassess the patient frequently to manage pain and withdrawal symptoms, should they emerge. Common withdrawal symptoms include restlessness, lacrimation, rhinorrhea, yawning, perspiration, chills, myalgia, and mydriasis. Other signs and symptoms also may develop, including irritability, anxiety, backache, joint pain, weakness, abdominal cramps, insomnia, nausea, anorexia, vomiting, diarrhea, or increased blood pressure, respiratory rate, or heart rate. If withdrawal symptoms arise, it may be necessary to pause the taper for a period of time or raise the dose of the opioid analgesic to the previous dose, and then proceed with a slower taper. In addition, evaluate patients for any changes in mood, emergence of suicidal thoughts, or use of other substances.

When managing patients taking opioid analgesics, particularly those who have been treated for an extended period of time, and/or with high doses for chronic pain, ensure that a multimodal approach to pain management, including mental health support (if needed), is in place prior to initiating an opioid analgesic taper. A multimodal approach to pain management may optimize the treatment of chronic pain, as well as assist with the successful tapering of the opioid analgesic *[see Warnings and Precautions (5.21), Drug Abuse and Dependence (9.3)]*.

3 DOSAGE FORMS AND STRENGTHS

Fentanyl transdermal systems are a rectangular, opaque patch with rounded corners:

- Fentanyl Transdermal System 12 mcg/hour* (system size 3.9 cm^2) is green in color.
- Fentanyl Transdermal System 25 mcg/hour (system size 7.8 cm^2) is green in color.
- Fentanyl Transdermal System 37.5 mcg/hour (system size 11.7 cm^2) is green in color.
- Fentanyl Transdermal System 50 mcg/hour (system size 15.6 cm^2) is green in color.
- Fentanyl Transdermal System 62.5 mcg/hour (system size 19.6 cm^2) is green in color.
- Fentanyl Transdermal System 75 mcg/hour (system size 23.4 cm^2) is green in color.
- Fentanyl Transdermal System 100 mcg/hour (system size 31.3 cm^2) is green in color.

* This lowest strength is designated as 12 mcg/hour (however, the actual strength is 12.5 mcg/hour) to distinguish it from a possible 125 mcg/hr dosage that could be prescribed by using multiple transdermal systems.

The 12 mcg/hour system has a green border and the 25, 37.5, 50, 62.5, 75 and 100 mcg/hour systems have green stripes that increase in number with each sequential increasing dosage strength.

4 CONTRAINDICATIONS

Fentanyl transdermal system is contraindicated in:

- patients who are not opioid-tolerant.
- the management of acute or intermittent pain, or in patients who require opioid analgesia for a short period of time.
- the management of post-operative pain, including use after out-patient or day surgeries, (e.g., tonsillectomies).
- the management of mild pain.
- patients with significant respiratory depression *[see Warnings and Precautions (5.12)]*.
- in patients with acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment *[see Warnings and Precautions (5.12)]*.
- in patients with known or suspected gastrointestinal obstruction, including paralytic ileus *[see Warnings and Precautions (5.19)]*.
- in patients with hypersensitivity to fentanyl (e.g., anaphylaxis) or any components of the transdermal system *[see Adverse Reactions (6.2)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Addiction, Abuse, and Misuse

Fentanyl transdermal system contains fentanyl, an opioid agonist and a Schedule II controlled substance. As an opioid, fentanyl transdermal system exposes users to the risks of addiction, abuse, and misuse.

Although the risk of addiction in any individual is unknown, it can occur in patients appropriately prescribed fentanyl transdermal system. Addiction can occur at recommended doses and if the drug is misused or abused. The risk of opioid-related overdose or overdose-related death is increased with higher opioid doses, and this risk persists over the course of therapy. In postmarketing studies, addiction, abuse, misuse, and fatal and non-fatal opioid overdose were observed in patients with long-term opioid use *[see Adverse Reactions (6.2)]*.

Assess each patient’s risk for opioid addiction, abuse, or misuse prior to prescribing fentanyl transdermal system, and reassess all patients receiving fentanyl transdermal system for the development of these behaviors and conditions. Risks are increased in patients with a personal or family history of substance abuse (including drug or alcohol abuse or addiction) or mental illness (e.g., major depression). The potential for these risks should not, however, prevent the proper management of pain in any given patient. Patients at increased risk may be prescribed opioids such as fentanyl transdermal system, but use in such patients necessitates intensive counseling about the risks and proper use of fentanyl transdermal system along with frequent reevaluation for signs of addiction, abuse, and misuse. Consider recommending or prescribing an opioid overdose reversal agent *[see Dosage and Administration (2.2), Warnings and Precautions (5.2)]*.

Abuse or misuse of fentanyl transdermal system by placing it in the mouth, chewing it, swallowing it, or using it in ways other than indicated may cause choking, overdose, and death *[see Overdosage (10)]*.

Opioids are sought for nonmedical use and are subject to diversion from legitimate prescribed use. Consider these risks when prescribing or dispensing fentanyl transdermal system. Strategies to reduce these risks include prescribing the drug in the

smallest appropriate quantity and advising the patient on careful storage of the drug during the course of treatment and proper disposal of unused drug. Contact local state professional licensing board or state-controlled substances authority for information on how to prevent and detect abuse or diversion of this product.

5.2 Life-Threatening Respiratory Depression

Serious, life-threatening, or fatal respiratory depression has been reported with the use of opioids, even when used as recommended. Respiratory depression, if not immediately recognized and treated, may lead to respiratory arrest and death. Management of respiratory depression may include close observation, supportive measures, and use of opioid overdose reversal agents, depending on the patient's clinical status *[see Overdosage (10)]*. Carbon dioxide (CO_2) retention from opioid-induced respiratory depression can exacerbate the sedating effects of opioids.

Fentanyl transdermal system is indicated only in opioid tolerant patients because of the risk for respiratory depression and death. While serious, life-threatening, or fatal respiratory depression can occur at any time during the use of fentanyl transdermal system, the risk is greatest during the initiation of therapy or following a dosage increase.

To reduce the risk of respiratory depression, proper dosing and titration of fentanyl transdermal system are essential *[see Dosage and Administration (2)]*. Overestimating the fentanyl transdermal system dosage when converting patients from another opioid product can result in fatal overdose with the first dose.

Accidental exposure to fentanyl transdermal system, especially in children, can result in respiratory depression and death due to an overdose of fentanyl.

Educate patients and caregivers on how to recognize respiratory depression and emphasize the importance of calling 911 or getting emergency medical help right away in the event of a known or suspected overdose *[see Patient Counseling Information (17)]*.

Opioids can cause sleep-related breathing disorders including central sleep apnea (CSA) and sleep-related hypoxemia. Opioid use increases the risk of CSA in a dose-dependent fashion. In patients who present with CSA, consider decreasing the opioid dosage using best practices for opioid taper *[see Dosage and Administration (2.9)]*.

Patient Access to an Opioid Overdose Reversal Agent for the Emergency Treatment of Opioid Overdose

Inform patients and caregivers about opioid overdose reversal agents (e.g., naloxone, nalmefene). Discuss the importance of having access to an opioid overdose reversal agent, especially if the patient has risk factors for overdose (e.g., concomitant use of CNS depressants, a history of opioid use disorder, or prior opioid overdose) or if there are household members (including children) or other close contacts at risk for accidental ingestion or opioid overdose. The presence of risk factors for overdose should not prevent the management of pain in any patient *[see Warnings and Precautions (5.1, 5.4)]*.

Discuss the options for obtaining an opioid overdose reversal agent (e.g., prescription, over-the-counter, or as part of a community-based program).

There are important differences among the opioid overdose reversal agents, such as route of administration, product strength, approved patient age range, and

pharmacokinetics. Be familiar with these differences, as outlined in the approved labeling for those products, prior to recommending or prescribing such an agent.

Educate patients and caregivers on how to recognize respiratory depression, and how to use an opioid overdose reversal agent for the emergency treatment of opioid overdose. Emphasize the importance of calling 911 or getting emergency medical help, even if an opioid overdose reversal agent is administered *[see Dosage and Administration (2.2), Warnings and Precautions (5.1, 5.4), Overdosage (10)]*.

5.3 Accidental Exposure

A considerable amount of active fentanyl remains in fentanyl transdermal system even after use as directed. Death and other serious medical problems have occurred when children and adults were accidentally exposed to fentanyl transdermal system. Accidental or deliberate application or ingestion by a child or adolescent will cause respiratory depression, and has resulted in deaths. Placing fentanyl transdermal system in the mouth, chewing it, swallowing it, or using it in ways other than indicated may cause choking or overdose that could result in death. Improper disposal of fentanyl transdermal system in the trash has resulted in accidental exposures and deaths.

Advise patients about strict adherence to the recommended handling and disposal instructions in order to prevent accidental exposure to fentanyl transdermal system *[see Dosage and Administration (2.7), (2.8)]*. Exposure to fentanyl transdermal systems discarded in the trash by children have been reported and have resulted in deaths.

5.4 Risks from Concomitant Use with Benzodiazepines or Other CNS Depressants

Profound sedation, respiratory depression, coma, and death may result from the concomitant use of fentanyl transdermal system with benzodiazepines and/or other CNS depressants, including alcohol [e.g., non-benzodiazepine sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, gabapentinoids (gabapentin or pregabalin), and other opioids]. Because of these risks, reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate.

Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of drug-related mortality compared to use of opioid analgesics alone. Because of similar pharmacological properties, it is reasonable to expect similar risk with the concomitant use of other CNS depressant drugs with opioid analgesics *[see Drug Interactions (7)]*.

If the decision is made to prescribe a benzodiazepine or other CNS depressant concomitantly with an opioid analgesic, prescribe the lowest effective dosages and minimum durations of concomitant use. In patients already receiving an opioid analgesic, prescribe a lower initial dose of the benzodiazepine or other CNS depressant than indicated in the absence of an opioid, and titrate based on clinical response. If an opioid analgesic is initiated in a patient already taking a benzodiazepine or other CNS depressant, prescribe a lower initial dose of the opioid analgesic, and titrate based on clinical response. Inform patients and caregivers of this potential interaction, educate

them on the signs and symptoms of respiratory depression (including sedation).

If concomitant use is warranted, consider recommending or prescribing an opioid overdose reversal agent *[see Dosage and Administration (2.2), Warnings and Precautions (5.2), Overdosage (10)]*.

Advise both patients and caregivers about the risks of respiratory depression and sedation when fentanyl transdermal system is used with benzodiazepines or other CNS depressants (including alcohol and illicit drugs). Advise patients not to drive or operate heavy machinery until the effects of concomitant use of the benzodiazepine or other CNS depressant have been determined. Screen patients for risk of substance use disorders, including opioid abuse and misuse, and warn them of the risk for overdose and death associated with the use of additional CNS depressants including alcohol and illicit drugs *[see Drug Interactions (7), Patient Counseling Information (17)]*.

5.5 Neonatal Opioid Withdrawal Syndrome

Use of fentanyl transdermal system for an extended period of time during pregnancy can result in withdrawal in the neonate. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. Observe newborns for signs of neonatal opioid withdrawal syndrome and manage accordingly. Advise pregnant women using opioids for an extended period of time of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available *[see Use in Specific Populations (8.1), Patient Counseling Information (17)]*.

5.6 Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS)

To ensure that the benefits of opioid analgesics outweigh the risks of addiction, abuse, and misuse, the Food and Drug Administration (FDA) has required a Risk Evaluation and Mitigation Strategy (REMS) for these products. Under the requirements of the REMS, drug companies with approved opioid analgesic products must make REMS-compliant education programs available to healthcare providers. Healthcare providers are strongly encouraged to do all of the following:

- Complete a REMS-compliant education program offered by an accredited provider of continuing education (CE) or another education program that includes all the elements of the FDA Education Blueprint for Health Care Providers Involved in the Management or Support of Patients with Pain.
- Discuss the safe use, serious risks, and proper storage and disposal of opioid analgesics with patients and/or their caregivers every time these medicines are prescribed. The Patient Counseling Guide (PCG) can be obtained at this link:www.fda.gov/OpioidAnalgesicREMSPCG.
- Emphasize to patients and their caregivers the importance of reading the Medication Guide that they will receive from their pharmacist every time an opioid analgesic is dispensed to them.
- Consider using other tools to improve patient, household, and community safety, such as patient-prescriber agreements that reinforce patient-prescriber responsibilities.

To obtain further information on the opioid analgesic REMS and for a list of accredited REMS CME/CE, call 1-800-503-0784, or log on to www.opioidanalgesicrems.com. The

FDA Blueprint can be found at www.fda.gov/OpioidAnalgesicREMSBlueprint.

5.7 Risks of Concomitant Use or Discontinuation of Cytochrome P450 3A4 Inhibitors and Inducers

Concomitant use of fentanyl transdermal system with a CYP3A4 inhibitor, such as macrolide antibiotics (e.g., erythromycin), azole-antifungal agents (e.g., ketoconazole), and protease inhibitors (e.g., ritonavir), may increase plasma concentrations of fentanyl and prolong opioid adverse reactions, which may cause potentially fatal respiratory depression *[see Warnings and Precautions (5.2)]*, particularly when an inhibitor is added after a stable dose of fentanyl transdermal system is achieved. Similarly, discontinuation of a CYP3A4 inducer, such as rifampin, carbamazepine, and phenytoin, in fentanyl transdermal system-treated patients may increase fentanyl plasma concentrations and prolong opioid adverse reactions. When using fentanyl transdermal system with CYP3A4 inhibitors or discontinuing CYP3A4 inducers in fentanyl transdermal system-treated patients, evaluate patients at frequent intervals and consider dosage reduction of fentanyl transdermal system until stable drug effects are achieved *[see Dosage and Administration (2.4), Drug Interactions (7)]*.

Concomitant use of fentanyl transdermal system with CYP3A4 inducers or discontinuation of a CYP3A4 inhibitor could decrease fentanyl transdermal system plasma concentrations, decrease opioid efficacy or, possibly, lead to a withdrawal syndrome in a patient who had developed physical dependence to fentanyl. When using fentanyl transdermal system with CYP3A4 inducers or discontinuing CYP3A4 inhibitors, monitor patients closely at frequent intervals and consider increasing the opioid dosage if needed to maintain adequate analgesia or if symptoms of opioid withdrawal occur *[see Drug Interactions (7)]*.

5.8 Risk of Increased Fentanyl Absorption with Application of External Heat

Exposure to heat may increase fentanyl absorption and there have been reports of overdose and death as a result of exposure to heat. A clinical pharmacology study conducted in healthy adult subjects has shown that the application of heat over the fentanyl transdermal system increased fentanyl exposure *[see Clinical Pharmacology (12.3)]*.

Warn patients to avoid exposing the fentanyl transdermal system application site and surrounding area to direct external heat sources *[see Dosage and Administration (2.7)]*.

5.9 Risk of Increased Fentanyl Absorption with Elevated Body Temperature

Based on a pharmacokinetic model, serum fentanyl concentrations could theoretically increase by approximately one-third for patients with a body temperature of 40°C (104°F) due to temperature-dependent increases in fentanyl released from the system and increased skin permeability. Monitor patients wearing fentanyl transdermal systems who develop fever closely for sedation and respiratory depression and reduce the fentanyl transdermal system dose, if necessary. Warn patients to avoid strenuous exertion that leads to increased core body temperature while wearing fentanyl transdermal system to avoid the risk of potential overdose and death.

5.10 Opioid-Induced Hyperalgesia and Allodynia

Opioid-Induced Hyperalgesia (OIH) occurs when an opioid analgesic paradoxically causes an increase in pain, or an increase in sensitivity to pain. This condition differs from tolerance, which is the need for increasing doses of opioids to maintain a defined effect *[see Dependence (9.3)].*

Symptoms of OIH include (but may not be limited to) increased levels of pain upon opioid dosage increase, decreased levels of pain upon opioid dosage decrease, or pain from ordinarily non-painful stimuli (allodynia). These symptoms may suggest OIH only if there is no evidence of underlying disease progression, opioid tolerance, opioid withdrawal, or addictive behavior.

Cases of OIH have been reported, both with short-term and longer-term use of opioid analgesics. Though the mechanism of OIH is not fully understood, multiple biochemical pathways have been implicated. Medical literature suggests a strong biologic plausibility between opioid analgesics and OIH and allodynia. If a patient is suspected to be experiencing OIH, carefully consider appropriately decreasing the dose of the current opioid analgesic, or opioid rotation (safely switching the patient to a different opioid moiety) *[see Dosage and Administration (2.9), Warnings and Precautions (5.21)]*.

5.11 Serotonin Syndrome with Concomitant Use of Serotonergic Drugs

Cases of serotonin syndrome, a potentially life-threatening condition, have been reported during concomitant use of fentanyl transdermal system with serotonergic drugs. Serotonergic drugs include selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), triptans, 5-HT3 receptor antagonists, drugs that affect the serotonergic neurotransmitter system (e.g., mirtazapine, trazodone, tramadol), certain muscle relaxants (i.e., cyclobenzaprine, metaxalone), and drugs that impair metabolism of serotonin (including MAO inhibitors, both those intended to treat psychiatric disorders and also others, such as linezolid and intravenous methylene blue) *[see Drug Interactions (7)]*. This may occur within the recommended dosage range. Serotonin syndrome symptoms may include mental status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g., hyperreflexia, incoordination, rigidity), and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea). The onset of symptoms generally occurs within several hours to a few days of concomitant use, but may occur later than that. Discontinue fentanyl transdermal system immediately if serotonin syndrome is suspected.

5.12 Life-Threatening Respiratory Depression in Patients with Chronic Pulmonary Disease or in Elderly, Cachectic, or Debilitated Patients

The use of fentanyl transdermal system in patients with acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment is contraindicated.

Patients with Chronic Pulmonary Disease: Fentanyl transdermal system-treated patients

with significant chronic obstructive pulmonary disease or cor pulmonale, and those with a substantially decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression are at increased risk of decreased respiratory drive including apnea, even at recommended dosages of fentanyl transdermal system *[see Warnings and Precautions (5.2)]*.

Elderly, Cachectic, or Debilitated Patients: Life-threatening respiratory depression is more likely to occur in elderly, cachectic, or debilitated patients because they may have altered pharmacokinetics or altered clearance compared to younger, healthier patients *[see Warnings and Precautions (5.2)]*.

Regularly evaluate patients, particularly when initiating and titrating fentanyl transdermal system and when fentanyl transdermal system is given concomitantly with other drugs that depress respiration *[see Warnings and Precautions (5.2)]*. Alternatively, consider the use of non-opioid analgesics in these patients.

5.13 Adrenal Insufficiency

Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use. Presentation of adrenal insufficiency may include non-specific symptoms and signs including nausea, vomiting, anorexia, fatigue, weakness, dizziness, and low blood pressure. If adrenal insufficiency is suspected, confirm the diagnosis with diagnostic testing as soon as possible. If adrenal insufficiency is diagnosed, treat with physiologic replacement doses of corticosteroids. Wean the patient off of the opioid to allow adrenal function to recover and continue corticosteroid treatment until adrenal function recovers. Other opioids may be tried as some cases reported use of a different opioid without recurrence of adrenal insufficiency. The information available does not identify any particular opioids as being more likely to be associated with adrenal insufficiency.

5.14 Severe Hypotension

Fentanyl transdermal system may cause severe hypotension including orthostatic hypotension and syncope in ambulatory patients. There is an increased risk in patients whose ability to maintain blood pressure has already been compromised by a reduced blood volume or concurrent administration of certain CNS depressant drugs (e.g., phenothiazines or general anesthetics) *[see Drug Interactions (7)]*. Regularly evaluate these patients for signs of hypotension after initiating or titrating the dosage of fentanyl transdermal system. In patients with circulatory shock, fentanyl transdermal system may cause vasodilation that can further reduce cardiac output and blood pressure. Avoid the use of fentanyl transdermal system in patients with circulatory shock.

5.15 Risks of Use in Patients with Increased Intracranial Pressure, Brain Tumors, Head Injury, or Impaired Consciousness

In patients who may be susceptible to the intracranial effects of CO_2 retention (e.g., those with evidence of increased intracranial pressure or brain tumors), fentanyl transdermal system may reduce respiratory drive, and the resultant CO_2 retention can further increase intracranial pressure. Monitor such patients for signs of sedation and respiratory depression, particularly when initiating therapy with fentanyl transdermal system.

Opioids may also obscure the clinical course in a patient with a head injury. Avoid the use of fentanyl transdermal system in patients with impaired consciousness or coma.

5.16 Cardiac Disease

Fentanyl transdermal system may produce bradycardia. Regularly evaluate patients with bradyarrhythmias closely for changes in heart rate, particularly when initiating therapy with fentanyl transdermal system.

5.17 Hepatic Impairment

A clinical pharmacology study with fentanyl transdermal system in patients with cirrhosis has shown that systemic fentanyl exposure increased in these patients. Because of the long half-life of fentanyl when administered as fentanyl transdermal system and hepatic metabolism of fentanyl, avoid use of fentanyl transdermal system in patients with severe hepatic impairment. Insufficient information exists to make precise dosing recommendations regarding the use of fentanyl transdermal system in patients with impaired hepatic function. Therefore, to avoid starting patients with mild to moderate hepatic impairment on too high of a dose, start with one half of the usual dosage of fentanyl transdermal system. Regularly evaluate for signs of sedation and respiratory depression, including at each dosage increase *[see Dosage and Administration (2.5), Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)]*.

5.18 Renal Impairment

A clinical pharmacology study with intravenous fentanyl in patients undergoing kidney transplantation has shown that patients with high blood urea nitrogen level had low fentanyl clearance. Because of the long half-life of fentanyl when administered as fentanyl transdermal system, avoid the use of fentanyl transdermal system in patients with severe renal impairment. Insufficient information exists to make precise dosing recommendations regarding the use of fentanyl transdermal system in patients with impaired renal function. Therefore, to avoid starting patients with mild to moderate renal impairment on too high of a dose, start with one-half of the usual dosage of fentanyl transdermal system. Regularly evaluate for signs of sedation and respiratory depression, including at each dosage increase *[see Dosage and Administration (2.6), Use in Specific Populations (8.7) and Clinical Pharmacology (12.3)]*.

5.19 Risks of Gastrointestinal Complications

Fentanyl transdermal system is contraindicated in patients with known or suspected gastrointestinal obstruction, including paralytic ileus.

The fentanyl in fentanyl transdermal system may cause spasm of the sphincter of Oddi. Opioids may cause increases in serum amylase. Regularly evaluate patients with biliary tract disease, including acute pancreatitis for worsening symptoms.

Cases of opioid-induced esophageal dysfunction (OIED) have been reported in patients taking opioids. The risk of OIED may increase as the dose and/or duration of opioids increases. Regularly evaluate patients for signs and symptoms of OIED (e.g., dysphagia, regurgitation, non-cardiac chest pain), and if necessary, adjust opioid therapy as clinically appropriate *[see Clinical Pharmacology (12.2)]*.

5.20 Increased Risk of Seizures in Patients with Seizure Disorders

The fentanyl in fentanyl transdermal system may increase the frequency of seizures in patients with seizure disorders, and may increase the risk of seizures occurring in other clinical settings associated with seizures. Regularly evaluate patients with a history of seizure disorders for worsened seizure control during fentanyl transdermal system therapy.

5.21 Withdrawal

Do not rapidly reduce or abruptly discontinue fentanyl transdermal system in a patient physically dependent on opioids. When discontinuing fentanyl transdermal system in a physically dependent patient, gradually taper the dosage. Rapid tapering of fentanyl transdermal system in a patient physically dependent on opioids may lead to a withdrawal syndrome and return of pain *[see Dosage and Administration (2.9), Drug Abuse and Dependence (9.3)]*.

Additionally, avoid the use of mixed agonist/antagonist (e.g., pentazocine, nalbuphine, and butorphanol) or partial agonist (e.g., buprenorphine) analgesics in patients who are receiving a full opioid agonist analgesic, including fentanyl transdermal system. In these patients, mixed agonist/antagonist and partial agonist analgesics may reduce the analgesic effect and/or may precipitate withdrawal symptoms *[see Drug Interactions (7)]*.

5.22 Risks of Driving and Operating Machinery

Fentanyl transdermal system may impair the mental or physical abilities required for the performance of potentially dangerous activities, such as driving a car or operating machinery. Warn patients not to drive or operate dangerous machinery unless they are tolerant to the effects of the fentanyl transdermal system and know how they will react to the medication *[see Patient Counseling Information (17)]*.

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed elsewhere in the labeling:

- Addiction, Abuse, and Misuse *[see Warnings and Precautions (5.1)]*
- Life-Threatening Respiratory Depression *[see Warnings and Precautions (5.2)]*
- Accidental Exposure *[see Warnings and Precautions (5.3)]*
- Neonatal Opioid Withdrawal Syndrome *[see Warnings and Precautions (5.5)]*
- Interactions with Benzodiazepines or Other Central Nervous System Depressants *[see Warnings and Precautions (5.4)]*
- Opioid-Induced Hyperalgesia and Allodynia *[see Warnings and Precautions (5.10)]*
- Serotonin Syndrome *[see Warnings and Precautions (5.11)]*
- Adrenal Insufficiency *[see Warnings and Precautions (5.13)]*
- Severe Hypotension *[see Warnings and Precautions (5.14)]*
- Gastrointestinal Adverse Reactions *[see Warnings and Precautions (5.19)]*
- Seizures *[see Warnings and Precautions (5.20)]*
- Withdrawal *[see Warnings and Precautions (5.21)]*

6.1 Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

The safety of fentanyl transdermal system was evaluated in 216 patients who took at least one dose of fentanyl transdermal system in a multicenter, double-blind, randomized, placebo-controlled clinical trial of fentanyl transdermal system. This trial examined patients over 40 years of age with severe pain induced by osteoarthritis of the hip or knee and who were in need of and waiting for joint replacement.

The most common adverse reactions (≥5%) in a double-blind, randomized, placebo-controlled clinical trial in patients with severe pain were nausea, vomiting, somnolence, dizziness, insomnia, constipation, hyperhidrosis, fatigue, feeling cold, and anorexia. Other common adverse reactions (≥5%) reported in clinical trials in patients with chronic malignant or nonmalignant pain were headache and diarrhea. Adverse reactions reported for ≥1% of fentanyl transdermal system-treated patients and with an incidence greater than placebo-treated patients are shown in Table 3.

The most common adverse reactions that were associated with discontinuation in patients with pain (causing discontinuation in ≥1% of patients) were depression, dizziness, somnolence, headache, nausea, vomiting, constipation, hyperhidrosis, and fatigue.

Table 3. Adverse Reactions Reported by ≥1% of Fentanyl Transdermal System-treated Patients and With an Incidence Greater Than Placebo-treated Patients in 1 Double-Blind, Placebo-Controlled Clinical Trial of Fentanyl Transdermal System

System/Organ ClassAdverse Reaction	Fentanyl Transdermal System%(N=216)	Placebo%(N=200)
Cardiac disorders		
Palpitations	4	1
Ear and labyrinth disorders		
Vertigo	2	1
Gastrointestinal disorders		
Nausea	41	17
Vomiting	26	3
Constipation	9	1
Abdominal pain upper	3	2
Dry mouth	2	0
General disorders and administration site conditions		
Fatigue	6	3
Feeling cold	6	2
Malaise	4	1
Asthenia	2	0
Edema peripheral	1	1
Metabolism and nutrition disorders		

Anorexia	5	0
Musculoskeletal and connective tissue disorders		
Muscle spasms	4	2
Nervous system disorders		
Somnolence	19	3
Dizziness	10	4
Psychiatric disorders		
Insomnia	10	7
Depression	1	0
Skin and subcutaneous tissue disorders		
Hyperhidrosis	6	1
Pruritus	3	2
Rash	2	1

Adverse reactions not reported in Table 3 that were reported by ≥1% of fentanyl transdermal system-treated adult and pediatric patients (N=1854) in 11 controlled and uncontrolled clinical trials of fentanyl transdermal system used for the treatment of chronic malignant or nonmalignant pain are shown in Table 4.

Table 4. Adverse Reactions Reported by ≥1% of Fentanyl Transdermal System-treated Patients in 11 Clinical Trials of Fentanyl Transdermal System

System/Organ Class Adverse Reaction	**Fentanyl Transdermal System % (N=1854)**
Gastrointestinal disorders	
Diarrhea	10
Abdominal pain	3
Immune system disorders	
Hypersensitivity	1
Nervous system disorders	
Headache	12
Tremor	3
Paresthesia	2
Psychiatric disorders	
Anxiety	3
Confusional state	2
Hallucination	1
Renal and urinary disorders	
Urinary retention	1
Skin and subcutaneous tissue disorders	
Erythema	1

The following adverse reactions occurred in adult and pediatric patients with an overall

frequency of <1% and are listed in descending frequency within each System/Organ Class:

Cardiac disorders: cyanosis

Eye disorders: miosis

Gastrointestinal disorders: subileus

General disorders and administration site conditions: application site reaction, influenza-like illness, application site hypersensitivity, drug withdrawal syndrome, application site dermatitis

Musculoskeletal and connective tissue disorders: muscle twitching

Nervous system disorders: hypoesthesia

Psychiatric disorders: disorientation, euphoric mood

Reproductive system and breast disorders: erectile dysfunction, sexual dysfunction

Respiratory, thoracic and mediastinal disorders: respiratory depression

Skin and subcutaneous tissue disorders: eczema, dermatitis allergic, dermatitis contact

Pediatrics

The safety of fentanyl transdermal system was evaluated in three open-label trials in 289 pediatric patients with chronic pain, 2 years of age through 18 years of age. Adverse reactions reported by ≥1% of fentanyl transdermal system-treated pediatric patients are shown in Table 5.

Table 5. Adverse Reactions Reported by ≥1% of Fentanyl Transdermal System-treated Pediatric Patients in 3 Clinical Trials of Fentanyl Transdermal System

System/Organ Class **Adverse Reaction**	**Fentanyl Transdermal System** **%** **(N=289)**
Gastrointestinal disorders	
Vomiting	34
Nausea	24
Constipation	13
Diarrhea	13
Abdominal pain	9
Abdominal pain upper	4
Dry mouth	2
General disorders and administration site conditions	
Edema peripheral	5
Fatigue	2
Application site reaction	1
Asthenia	1
Immune system disorders	

Hypersensitivity	3
Metabolism and nutrition disorders	
Anorexia	4
Musculoskeletal and connective tissue disorders	
Muscle spasms	2
Nervous system disorders	
Headache	16
Somnolence	5
Dizziness	2
Tremor	2
Hypoesthesia	1
Psychiatric disorders	
Insomnia	6
Anxiety	4
Depression	2
Hallucination	2
Renal and urinary disorders	
Urinary retention	3
Respiratory, thoracic and mediastinal disorders	
Respiratory depression	1
Skin and subcutaneous tissue disorders	
Pruritus	13
Rash	6
Hyperhidrosis	3
Erythema	3

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of fentanyl transdermal system. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Cardiac Disorders: tachycardia, bradycardia

Eye Disorders: vision blurred

Gastrointestinal Disorders: ileus, dyspepsia

General Disorders and Administration Site Conditions: pyrexia, application site erosion and application site ulcer

Investigations: weight decreased

Nervous System Disorders: convulsions (including clonic convulsions and grand mal convulsion), amnesia, depressed level of consciousness, loss of consciousness

Psychiatric Disorders: agitation

Respiratory, Thoracic, and Mediastinal Disorders: respiratory distress, apnea, bradypnea, hypoventilation, dyspnea

Vascular Disorders: hypotension, hypertension

Serotonin syndrome: Cases of serotonin syndrome, a potentially life-threatening condition, have been reported during concomitant use of opioids with serotonergic drugs.

Adrenal insufficiency: Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use.

Anaphylaxis: Anaphylaxis, including anaphylactic shock, has been reported with ingredients contained in fentanyl transdermal system.

Androgen deficiency: Cases of androgen deficiency have occurred with use of opioids for an extended period of time *[see Clinical Pharmacology (12.2)]*.

Hyperalgesia and Allodynia: Cases of hyperalgesia and allodynia have been reported with opioid therapy of any duration *[see Warnings and Precautions (5.10)]*.

Hypoglycemia: Cases of hypoglycemia have been reported in patients taking opioids. Most reports were in patients with at least one predisposing risk factor (e.g., diabetes).

Opioid-induced esophageal dysfunction (OIED): Cases of OIED have been reported in patients taking opioids, and may occur more frequently in patients taking higher doses of opioids, and/or in patients taking opioids longer term *[see Warnings and Precautions (5.19)]*.

Adverse Reactions from Observational Studies

A prospective, observational cohort study estimated the risks of addiction, abuse, and misuse in patients initiating long-term use of Schedule II opioid analgesics between 2017 and 2021. Study participants included in one or more analyses had been enrolled in selected insurance plans or health systems for at least one year, were free of at least one outcome at baseline, completed a minimum number of follow-up assessments, and either: 1) filled multiple extended-release/long-acting opioid analgesic prescriptions during a 90-day period (n=978); or 2) filled any Schedule II opioid analgesic prescriptions covering at least 70 of 90 days (n=1,244). Those included also had no dispensing of the qualifying opioids in the previous 6 months.

Over 12 months:

- approximately 1% to 6% of participants across the two cohorts newly met criteria for addiction, as assessed with two validated interview-based measures of moderate-to-severe opioid use disorder based on Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria, and
- approximately 9% and 22% of participants across the two cohorts newly met criteria for prescription opioid abuse and misuse *[defined in Drug Abuse and Dependence (9.2)]*, respectively, as measured with a validated self-reported instrument.

A retrospective, observational cohort study estimated the risk of opioid-involved overdose or opioid overdose-related death in patients with new long-term use of Schedule II opioid analgesics from 2006 through 2016 (n=220,249). Included patients had been enrolled in either one of two commercial insurance programs, one managed care program, or one Medicaid program for at least 9 months. *New long-term use* was defined as having Schedule II opioid analgesic prescriptions covering at least 70 days' supply over the 3 months prior to study entry and none during the preceding 6 months. Patients were excluded if they had an opioid-involved overdose in the 9 months prior to

study entry. Overdose was measured using a validated medical code-based algorithm with linkage to the National Death Index database. The 5-year cumulative incidence estimates for opioid-involved overdose or opioid overdose-related death ranged from approximately 1.5% to 4% across study sites, counting only the first event during follow-up. Approximately 17% of first opioid overdoses observed over the entire study period (5-11 years, depending on the study site) were fatal. Higher baseline opioid dose was the strongest and most consistent predictor of opioid-involved overdose or opioid overdose-related death. Study exclusion criteria may have selected patients at lower risk of overdose, and substantial loss to follow-up (approximately 80%) also may have biased estimates.

The risk estimates from the studies described above may not be generalizable to all patients receiving opioid analgesics, such as those with exposures shorter or longer than the duration evaluated in the studies.

7 DRUG INTERACTIONS

Table 6 includes clinically significant drug interactions with fentanyl transdermal system.

Table 6. Clinically Significant Drug Interactions with Fentanyl Transdermal System

Inhibitors of CYP3A4	
Clinical Impact:	The concomitant use of fentanyl transdermal system and CYP3A4 inhibitors can increase the plasma concentration of fentanyl, resulting in increased or prolonged opioid effects particularly when an inhibitor is added after a stable dose of fentanyl transdermal system is achieved *[see Warnings and Precautions (5.7)]*. After stopping a CYP3A4 inhibitor, as the effects of the inhibitor decline, the fentanyl transdermal system plasma concentration will decrease *[see Clinical Pharmacology (12.3)]*, resulting in decreased opioid efficacy or a withdrawal syndrome in patients who had developed physical dependence to fentanyl.
Intervention:	If concomitant use is necessary, consider dosage reduction of fentanyl transdermal system until stable drug effects are achieved. Evaluate patients at frequent intervals for respiratory depression and sedation. If a CYP3A4 inhibitor is discontinued, consider increasing the fentanyl transdermal system dosage until stable drug effects are achieved. Evaluate for signs of opioid withdrawal.
Examples:	Macrolide antibiotics (e.g., erythromycin), azole-antifungal agents (e.g., ketoconazole), protease inhibitors (e.g., ritonavir), grapefruit juice
CYP3A4 Inducers	
Clinical Impact:	The concomitant use of fentanyl transdermal system and CYP3A4 inducers can decrease the plasma concentration of fentanyl *[see Clinical Pharmacology (12.3)]*, resulting in decreased efficacy or onset of a withdrawal syndrome in patients who have developed physical dependence to fentanyl *[see Warnings and Precautions (5.7)]*.

	After stopping a CYP3A4 inducer, as the effects of the inducer decline, the fentanyl plasma concentration will increase *[see Clinical Pharmacology (12.3)]*, which could increase or prolong both the therapeutic effects and adverse reactions, and may cause serious respiratory depression.
Intervention:	If concomitant use is necessary, consider increasing the fentanyl transdermal system dosage until stable drug effects are achieved. Evaluate for signs of opioid withdrawal. If a CYP3A4 inducer is discontinued, consider fentanyl transdermal system dosage reduction and evaluate patients at frequent intervals for signs of respiratory depression and sedation.
Examples:	Rifampin, carbamazepine, phenytoin
Benzodiazepines and Other Central Nervous System (CNS) Depressants	
Clinical Impact:	Due to additive pharmacologic effect, the concomitant use of benzodiazepines or other CNS depressants, including alcohol, can increase the risk of hypotension, respiratory depression, profound sedation, coma, and death.
Intervention:	Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate. Limit dosages and durations to the minimum required. Inform patients and caregivers of this potential interaction, educate them on the signs and symptoms of respiratory depression (including sedation). If concomitant use is warranted, consider recommending or prescribing an opioid overdose reversal agent *[see Dosage and Administration (2.2), Warnings and Precautions (5.1, 5.2, 5.4)]*.
Examples:	Benzodiazepines and other sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, gabapentinoids (gabapentin or pregabalin), other opioids, alcohol.
Serotonergic Drugs	
Clinical Impact:	The concomitant use of opioids with other drugs that affect the serotonergic neurotransmitter system has resulted in serotonin syndrome *[see Warnings and Precautions (5.11)].*
Intervention:	If concomitant use is warranted, frequently evaluate the patient, particularly during treatment initiation and dose adjustment. Discontinue fentanyl transdermal system if serotonin syndrome is suspected.
Examples:	Selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), triptans, 5-HT3 receptor antagonists, drugs that affect the serotonin neurotransmitter system (e.g., mirtazapine, trazodone, tramadol), certain muscle relaxants (i.e., cyclobenzaprine, metaxalone), monoamine oxidase (MAO) inhibitors (those intended to treat psychiatric disorders and also others, such as linezolid and intravenous methylene blue).
Monoamine Oxidase Inhibitors (MAOIs)	
Clinical Impact:	MAOI interactions with opioids may manifest as serotonin syndrome *[see Warnings and Precautions (5.11)]* or opioid toxicity (e.g., respiratory depression, coma).
Intervention:	The use of fentanyl transdermal system is not recommended for patients taking MAOIs or within 14 days of stopping such treatment.
Examples:	phenelzine, tranylcypromine, linezolid

Mixed Agonist/Antagonist and Partial Agonist Opioid Analgesics	
Clinical Impact:	May reduce the analgesic effect of fentanyl transdermal system and/or precipitate withdrawal symptoms.
Intervention:	Avoid concomitant use.
Examples:	butorphanol, nalbuphine, pentazocine, buprenorphine
Muscle Relaxants	
Clinical Impact:	Fentanyl transdermal system may enhance the neuromuscular blocking action of skeletal muscle relaxants and produce an increased degree of respiratory depression.
Intervention:	Because respiratory depression may be greater than otherwise expected, decrease the dosage of fentanyl transdermal system and/or the muscle relaxant as necessary. Due to the risk of respiratory depression with concomitant use of skeletal muscle relaxants and opioids, consider recommending or prescribing an opioid overdose reversal agent *[see Dosage and Administration (2.2), Warnings and Precautions (5.2, 5.4)]*.
Examples:	cyclobenzaprine, metaxalone
Diuretics	
Clinical Impact:	Opioids can reduce the efficacy of diuretics by inducing the release of antidiuretic hormone.
Intervention:	Evaluate patients for signs of diminished diuresis and/or effects on blood pressure and increase the dosage of the diuretic as needed.
Anticholinergic Drugs	
Clinical Impact:	The concomitant use of anticholinergic drugs may increase risk of urinary retention and/or severe constipation, which may lead to paralytic ileus.
Intervention:	Evaluate patients for signs of urinary retention or reduced gastric motility when fentanyl transdermal system is used concomitantly with anticholinergic drugs.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Use of opioid analgesics for an extended period of time during pregnancy may cause neonatal opioid withdrawal syndrome *[see Warnings and Precautions (5.5)]*. Available data with fentanyl transdermal system in pregnant women are insufficient to inform a drug-associated risk for major birth defects and miscarriage.

In animal reproduction studies, fentanyl administration to pregnant rats during organogenesis was embryocidal at doses within the range of the human recommended dosing. When administered during gestation through lactation fentanyl administration to pregnant rats resulted in reduced pup survival and developmental delays at doses within the range of the human recommended dosing. No evidence of malformations were noted in animal studies completed to date *[see Data]*.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or

other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Clinical Considerations

Fetal/Neonatal Adverse Reactions

Use of opioid analgesics for an extended period of time during pregnancy for medical or nonmedical purposes can result in physical dependence in the neonate and neonatal opioid withdrawal syndrome shortly after birth. Neonatal opioid withdrawal syndrome presents as irritability, hyperactivity and abnormal sleep pattern, high pitched cry, tremor, vomiting, diarrhea, and failure to gain weight. The onset, duration, and severity of neonatal opioid withdrawal syndrome vary based on the specific opioid used, duration of use, timing and amount of last maternal use, and rate of elimination of the drug by the newborn. Observe newborns for symptoms of neonatal opioid withdrawal syndrome and manage accordingly *[see Warnings and Precautions (5.5)]*.

Labor or Delivery

Opioids cross the placenta and may produce respiratory depression and psycho-physiologic effects in neonates. An opioid overdose reversal agent, such as naloxone or nalmefene, must be available for reversal of opioid-induced respiratory depression in the neonate. Fentanyl transdermal system is not recommended for use in pregnant women during or immediately prior to labor, when use of shorter-acting analgesics or other analgesic techniques are more appropriate. Opioid analgesics, including fentanyl transdermal system, can prolong labor through actions that temporarily reduce the strength, duration, and frequency of uterine contractions. However, this effect is not consistent and may be offset by an increased rate of cervical dilatation, which tends to shorten labor. Monitor neonates exposed to opioid analgesics during labor for signs of excess sedation and respiratory depression.

Data

Human Data

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.

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

Animal Data

No evidence of malformations or adverse effects on the fetus was reported in a published study in which pregnant rats were administered fentanyl continuously via subcutaneously implanted osmotic minipumps at doses of 10, 100, or 500 mcg/kg/day starting 2 weeks prior to breeding and throughout pregnancy. The high dose was approximately 2 times the daily human dose administered by a 100 mcg/hr patch on a mg/m^2 basis).

In contrast, the intravenous administration of fentanyl (0, 0.01, or 0.03 mg/kg) to

pregnant rats from Gestation Day 6 to 18 suggested evidence of embryo-toxicity and a slight increase in mean delivery time in the 0.03 mg/kg/day group (0.1 times the human dose administered by a 100 mcg/hr patch on a mg/m^2 basis). There was no clear evidence of teratogenicity noted.

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

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

8.2 Lactation

Risk Summary
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.

Because of the potential for serious adverse reactions, including excess sedation and respiratory depression in a breastfed infant, advise patients that breastfeeding is not recommended during treatment with fentanyl transdermal system.

Clinical Considerations
Monitor infants exposed to fentanyl transdermal system through breast milk for excess sedation and respiratory depression. Withdrawal symptoms can occur in breastfed infants when maternal administration of an opioid analgesic is stopped, or when breast-feeding is stopped.

8.3 Females and Males of Reproductive Potential

Infertility
Use of opioids for an extended period of time may cause reduced fertility in females and males of reproductive potential. It is not known whether these effects on fertility are reversible *[see Adverse Reactions (6.2), Clinical Pharmacology (12.2) and Nonclinical Toxicology (13.1)]*.

8.4 Pediatric Use

The safety of fentanyl transdermal system was evaluated in three open-label trials in 289

pediatric patients with chronic pain, 2 years of age through 18 years of age. Starting doses of 25 mcg/hr and higher were used by 181 patients who had been on prior daily opioid doses of at least 45 mg/day of oral morphine or an equianalgesic dose of another opioid. Initiation of fentanyl transdermal system therapy in pediatric patients taking less than 60 mg/day of oral morphine or an equianalgesic dose of another opioid has not been evaluated in controlled clinical trials.

The safety and effectiveness of fentanyl transdermal system in children under 2 years of age have not been established.

To guard against excessive exposure to fentanyl transdermal system by young children, advise caregivers to strictly adhere to recommended fentanyl transdermal system application and disposal instructions *[see Dosage and Administration (2.7), (2.8) and Warnings and Precautions (5.3)]*.

8.5 Geriatric Use

Clinical studies of fentanyl transdermal system did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, use caution when selecting a dosage for an elderly patient, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

Data from intravenous studies with fentanyl suggest that the elderly patients may have reduced clearance and a prolonged half-life. Moreover, elderly patients may be more sensitive to the active substance than younger patients. A study conducted with the fentanyl transdermal system in elderly patients demonstrated that fentanyl pharmacokinetics did not differ significantly from young adult subjects, although peak serum concentrations tended to be lower and mean half-life values were prolonged to approximately 34 hours *[see Clinical Pharmacology (12.3)]*.

Respiratory depression is the chief risk for elderly patients treated with opioids, and has occurred after large initial doses were administered to patients who were not opioid-tolerant or when opioids were co-administered with other agents that depress respiration. Titrate the dosage of fentanyl transdermal system slowly in geriatric patients and frequently reevaluate the patient for signs of central nervous system and respiratory depression *[see Warnings and Precautions (5.12)]*.

Fentanyl is known to be substantially excreted by the kidney, and the risk of adverse reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to regularly evaluate renal function.

8.6 Hepatic Impairment

The effect of hepatic impairment on the pharmacokinetics of fentanyl transdermal system has not been fully evaluated. A clinical pharmacology study with fentanyl transdermal system in patients with cirrhosis has shown that systemic fentanyl exposure increased in these patients. Because there is *in-vitro* and *in-vivo* evidence of extensive hepatic contribution to the elimination of fentanyl transdermal system, hepatic

impairment would be expected to have significant effects on the pharmacokinetics of fentanyl transdermal system. Avoid use of fentanyl transdermal system in patients with severe hepatic impairment *[see Dosage and Administration (2.5), Warnings and Precautions (5.17) and Clinical Pharmacology (12.3)]*.

8.7 Renal Impairment

The effect of renal impairment on the pharmacokinetics of fentanyl transdermal system has not been fully evaluated. A clinical pharmacology study with intravenous fentanyl in patients undergoing kidney transplantation has shown that patients with high blood urea nitrogen level had low fentanyl clearance. Because there is *in-vivo* evidence of renal contribution to the elimination of fentanyl transdermal system, renal impairment would be expected to have significant effects on the pharmacokinetics of fentanyl transdermal system. Avoid the use of fentanyl transdermal system in patients with severe renal impairment *[see Dosage and Administration (2.6), Warnings and Precautions (5.18) and Clinical Pharmacology (12.3)].*

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

Fentanyl transdermal system contains fentanyl, a Schedule II controlled substance.

9.2 Abuse

Fentanyl transdermal system contains fentanyl, a substance with high potential for misuse and abuse, which can lead to the development of substance use disorder, including addiction *[see Warnings and Precautions (5.1)].*

Misuse is the intentional use, for therapeutic purposes, of a drug by an individual in a way other than prescribed by a healthcare provider or for whom it was not prescribed.

Abuse is the intentional, non-therapeutic use of a drug, even once, for its desirable psychological or physiological effects.

Drug addiction is a cluster of behavioral, cognitive, and physiological phenomena that may include a strong desire to take the drug, difficulties in controlling drug use (e.g., continuing drug use despite harmful consequences, giving a higher priority to drug use than other activities and obligations), and possible tolerance or physical dependence.

Misuse and abuse of fentanyl transdermal system increases risk of overdose, which may lead to central nervous system and respiratory depression, hypotension, seizures, and death. The risk is increased with concurrent abuse of fentanyl transdermal system with alcohol and other CNS depressants. Abuse of and addiction to opioids in some individuals may not be accompanied by concurrent tolerance and symptoms of physical dependence. In addition, abuse of opioids can occur in the absence of addiction.

All patients treated with opioids require careful and frequent reevaluation for signs of misuse, abuse, and addiction, because use of opioid analgesic products carries the risk of addiction even under appropriate medical use. Patients at high risk of fentanyl transdermal system abuse include those with a history of prolonged use of any opioid, including products containing fentanyl, those with a history of drug or alcohol abuse, or those who use fentanyl transdermal system in combination with other abused drugs.

“Drug-seeking” behavior is very common in persons with substance use disorders. Drug-seeking tactics include emergency calls or visits near the end of office hours, refusal to undergo appropriate examination, testing, or referral, repeated “loss” of prescriptions, tampering with prescriptions, and reluctance to provide prior medical records or contact information for other treating healthcare provider(s). “Doctor shopping” (visiting multiple prescribers to obtain additional prescriptions) is common among people who abuse drugs and people with substance use disorder. Preoccupation with achieving adequate pain relief can be appropriate behavior in a patient with inadequate pain control.

Fentanyl transdermal system, like other opioids, can be diverted for nonmedical use into illicit channels of distribution. Careful record-keeping of prescribing information, including quantity, frequency, and renewal requests, as required by state and federal law, is strongly advised.

Proper assessment of the patient, proper prescribing practices, periodic reevaluation of therapy, and proper dispensing and storage are appropriate measures that help to limit abuse of opioid drugs.

Risks Specific to the Abuse of Fentanyl Transdermal System
Fentanyl transdermal system is intended for transdermal use only. Abuse of fentanyl transdermal system poses a risk of overdose and death. This risk is increased with concurrent use of fentanyl transdermal system with alcohol and/or other CNS depressants *[see Warnings and Precautions (5.4), Drug Interactions (7)]*. Intentional compromise of the transdermal delivery system may result in the uncontrolled delivery of fentanyl and pose a significant risk to the abuser that could result in overdose and death *[see Warnings and Precautions (5.1)]*. Abuse may occur by applying the transdermal system in the absence of legitimate purpose, or by swallowing, snorting or injecting fentanyl extracted from the transdermal system.

9.3 Dependence

Both tolerance and physical dependence can develop during use of opioid therapy.

Tolerance is a physiological state characterized by a reduced response to a drug after repeated administration (i.e., a higher dose of a drug is required to produce the same effect that was once obtained at a lower dose).

Physical dependence is a state that develops as a result of a physiological adaptation in response to repeated drug use, manifested by withdrawal signs and symptoms after abrupt discontinuation or a significant dose reduction of a drug.

Withdrawal may be precipitated through the administration of drugs with opioid antagonist activity (e.g., naloxone, nalmefene), mixed agonist/antagonist analgesics (e.g., pentazocine, butorphanol, nalbuphine), or partial agonists (e.g., buprenorphine). Physical dependence may not occur to a clinically significant degree until after several days to weeks of continued use.

Do not rapidly reduce or abruptly discontinue fentanyl transdermal system in a patient physically dependent on opioids. Rapid reduction or abrupt discontinuation of fentanyl transdermal system in a patient physically dependent on opioids may lead to serious withdrawal symptoms, uncontrolled pain, and suicide. Rapid reduction or abrupt discontinuation has also been associated with attempts to find other sources of opioid analgesics, which may be confused with drug-seeking for abuse.

When discontinuing fentanyl transdermal system, gradually taper the dosage using a patient-specific plan that considers the following: the dose of fentanyl transdermal system the patient has been taking, the duration of treatment, and the physical and psychological attributes of the patient. To improve the likelihood of a successful taper and minimize withdrawal symptoms, it is important that the opioid tapering schedule is agreed upon by the patient. In patients taking opioids for an extended period of time at high doses, ensure that a multimodal approach to pain management, including mental health support (if needed), is in place prior to initiating an opioid analgesic taper *[see Dosage and Administration (2.9), Warnings and Precautions (5.21)].*

Infants born to mothers physically dependent on opioids will also be physically dependent and may exhibit respiratory difficulties and withdrawal signs *[see Use in Specific Populations (8.1)].*

10 OVERDOSAGE

Clinical Presentation

Acute overdose with fentanyl transdermal system can be manifested by respiratory depression, somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, constricted pupils, and, in some cases, pulmonary edema, bradycardia, hypotension, hypoglycemia, partial or complete airway obstruction, atypical snoring, and death. Marked mydriasis rather than miosis may be seen with hypoxia in overdose situations *[see Clinical Pharmacology (12.2)]*. Toxic leukoencephalopathy has been reported after opioid overdose and can present hours, days, or weeks after apparent recovery from the initial intoxication.

Treatment of Overdose

Give primary attention to the reestablishment of a patent airway and institution of assisted or controlled ventilation, if needed. Employ other supportive measures (including oxygen and vasopressors) in the management of circulatory shock and pulmonary edema as indicated. Cardiac arrest or arrhythmias will require advanced life support measures. Once stable, examine the patient and ensure that all fentanyl transdermal systems have been removed.

For clinically significant respiratory or circulatory depression secondary to opioid overdose, administer an opioid overdose reversal agent such as naloxone or nalmefene.

Because the duration of opioid reversal is expected to be less than the duration of action of fentanyl in fentanyl transdermal systems, carefully monitor the patient until spontaneous respiration is reliably reestablished. After fentanyl transdermal system removal, serum fentanyl concentrations decline gradually, falling about 50% in approximately 20 to 27 hours. Therefore, management of an overdose must be monitored accordingly, at least 72 to 96 hours beyond the overdose.

In an individual physically dependent on opioids, administration of the recommended usual dosage of the opioid overdose reversal agent will precipitate an acute withdrawal syndrome. The severity of the withdrawal symptoms experienced will depend on the degree of physical dependence and the dose of the reversal agent administered. If a decision is made to treat serious respiratory depression in the physically-dependent patient, administration of the reversal agent should be initiated with care and by titration with smaller than usual doses of the reversal agent.

11 DESCRIPTION

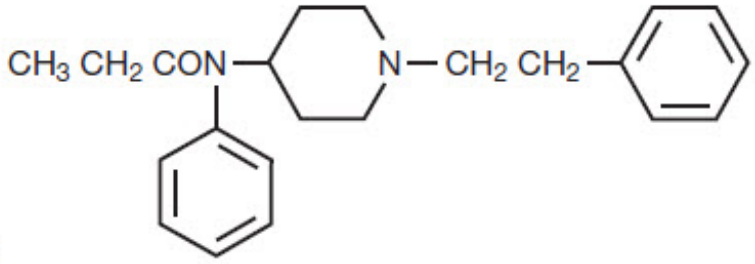
Fentanyl transdermal system contains fentanyl, an opioid agonist, available as a patch for transdermal administration. The amount of fentanyl released from each system per hour is proportional to the surface area (25 mcg/hr per 7.8 cm^2). The composition per unit area of all system sizes is identical.

Strength (mcg/hr)	Size (cm^2)	Fentanyl Content (mg)	Color of Printing on Back of Patch
12*	3.9	1.375	Green
25†	7.8	2.75	Green
37.5†	11.7	4.125	Green
50†	15.6	5.50	Green
62.5†	19.6	6.875	Green
75†	23.4	8.25	Green
100†	31.3	11.0	Green

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

The n-octanol: water partition coefficient is 860:1. The pKa is 8.4.

The chemical name is N-Phenyl-N-(1-(2-phenylethyl)-4-piperidinyl) propanamide. The structural formula is:



$C_{22}H_{28}N_2O$ MW=336.5

Fentanyl transdermal systems are a rectangular, opaque patch with rounded corners:

- 12 mcg/hr: Fentanyl Transdermal System 12 mcg/hr printed in green
- 25 mcg/hr: Fentanyl Transdermal System 25 mcg/hr printed in green
- 37.5 mcg/hr: Fentanyl Transdermal System 37.5 mcg/hr printed in green
- 50 mcg/hr: Fentanyl Transdermal System 50 mcg/hr printed in green
- 62.5 mcg/hr: Fentanyl Transdermal System 62.5 mcg/hr printed in green
- 75 mcg/hr: Fentanyl Transdermal System 75 mcg/hr printed in green
- 100 mcg/hr: Fentanyl Transdermal System 100 mcg/hr printed in green

The 12 mcg/hour system has a green border and the 25, 37.5, 50, 62.5, 75 and 100 mcg/hour systems have green stripes that increase in number with each sequential increasing dosage strength.

Fentanyl transdermal system is a rectangular opaque unit comprising a protective liner

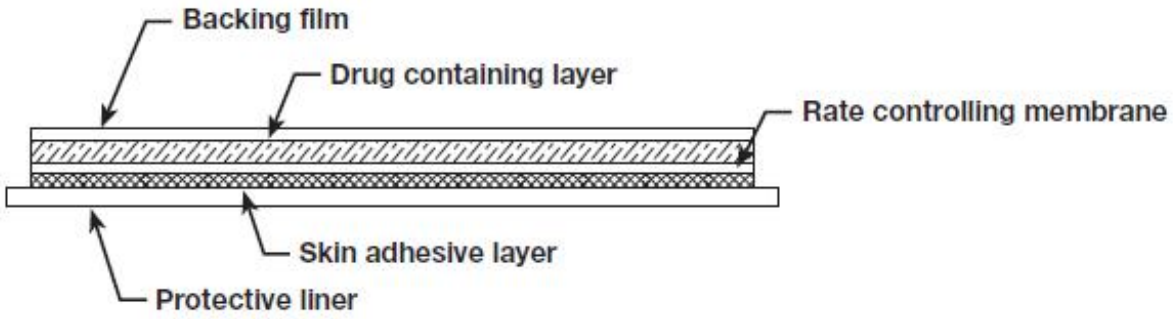
and four functional layers. Proceeding from the outer surface toward the surface adhering to skin, these layers are:

1) a backing layer of PET foil;

2) a drug containing layer of fentanyl and dipropylene glycol with hydroxypropyl cellulose;

3) an ethylene vinyl-acetate copolymer membrane that controls the rate of fentanyl delivery to the skin surface; and

4) a silicone adhesive. Before use, a protective liner covering the adhesive layer is removed and discarded.



12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

12.2 Pharmacodynamics

Effects on the Central Nervous System
Fentanyl produces respiratory depression by direct action on brain stem respiratory centers. The respiratory depression involves a reduction in the responsiveness of the brain stem respiratory centers to both increases in carbon dioxide tension and electrical stimulation.

Fentanyl causes miosis, even in total darkness. Pinpoint pupils are a sign of opioid overdose but are not pathognomonic (e.g., pontine lesions of hemorrhagic or ischemic origins may produce similar findings). Marked mydriasis rather than miosis may be seen due to hypoxia in overdose situations.

In clinical trials of 357 non-opioid tolerant subjects treated with fentanyl transdermal system, 13 subjects experienced hypoventilation. Hypoventilation was manifested by respiratory rates of less than 8 breaths/minute or a pCO_2 greater than 55 mm Hg. In these studies, the incidence of hypoventilation was higher in nontolerant women (10) than in men (3) and in subjects weighing less than 63 kg (9 of 13). Although subjects with prior impaired respiration were not common in the trials, they had higher rates of hypoventilation. In addition, postmarketing reports have been received that describe opioid-naive post-operative patients who have experienced clinically significant

hypoventilation and death with fentanyl transdermal system.

Hypoventilation can occur throughout the therapeutic range of fentanyl serum concentrations, especially for patients who have an underlying pulmonary condition or who receive concomitant opioids or other CNS drugs associated with hypoventilation. The use of fentanyl transdermal system is contraindicated in patients who are not tolerant to opioid therapy.

Effects on the Gastrointestinal Tract and Other Smooth Muscle
Fentanyl causes a reduction in motility associated with an increase in smooth muscle tone in the antrum of the stomach and duodenum. Digestion of food in the small intestine is delayed and propulsive contractions are decreased. Propulsive peristaltic waves in the colon are decreased, while tone is increased to the point of spasm, resulting in constipation. Other opioid-induced effects may include a reduction in biliary and pancreatic secretions, spasm of sphincter of Oddi, transient elevations in serum amylase, and opioid-induced esophageal dysfunction (OIED).

Effects on the Cardiovascular System
Fentanyl produces peripheral vasodilation, which may result in orthostatic hypotension or syncope. Manifestations of histamine release and/or peripheral vasodilation may include pruritus, flushing, red eyes, sweating, and/or orthostatic hypotension.

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

Effects on the Endocrine System
Opioids inhibit the secretion of adrenocorticotropic hormone (ACTH), cortisol, and luteinizing hormone (LH) in humans *[see Adverse Reactions (6.2)]*. They also stimulate prolactin, growth hormone (GH) secretion, and pancreatic secretion of insulin and glucagon.

Use of opioids for an extended period of time may influence the hypothalamic-pituitary-gonadal axis, leading to androgen deficiency that may manifest as low libido, impotence, erectile dysfunction, amenorrhea, or infertility. The causal role of opioids in the clinical syndrome of hypogonadism is unknown because the various medical, physical, lifestyle, and psychological stressors that may influence gonadal hormone levels have not been adequately controlled for in studies conducted to date *[see Adverse Reactions (6.2)]*.

Effects on the Immune System
Opioids have been shown to have a variety of effects on components of the immune system in *in vitro* and animal models. The clinical significance of these findings is unknown. Overall, the effects of opioids appear to be modestly immunosuppressive.

Concentration-Efficacy Relationships
The minimum effective analgesic concentration will vary widely among patients, especially among patients who have been previously treated with opioid agonists. The minimum effective analgesic concentration of fentanyl for any individual patient may increase over time due to an increase in pain, the development of a new pain syndrome, and/or the development of analgesic tolerance *[see Dosage and Administration (2.1, 2.4)]*.

Concentration-Adverse Reaction Relationships
There is a relationship between increasing fentanyl plasma concentration and increasing frequency of dose-related opioid adverse reactions such as nausea, vomiting, CNS

effects, and respiratory depression. In opioid-tolerant patients, the situation may be altered by the development of tolerance to opioid-related adverse reactions *[see Dosage and Administration (2.1, 2.3, 2.4)]*.

12.3 Pharmacokinetics

Absorption

Fentanyl transdermal system is a drug-in-adhesive matrix designed formulation. Fentanyl is released from the matrix at a nearly constant amount per unit time. The concentration gradient existing between the 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 matrix and the diffusion of fentanyl through the skin layers. While the actual rate of fentanyl delivery to the skin varies over the 72-hour application period, each system is labeled with a nominal flux which represents the average amount of drug delivered to the systemic circulation per hour across average skin.

While there is variation in dose delivered among patients, the nominal flux of the systems (12.5, 25, 37.5, 50, 62.5, 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 the 72-hour application period. Peak serum concentrations of fentanyl generally occurred between 20 and 72 hours after initial application (*see* Table 7). 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 two system applications. By the end of the second 72-hour application, a steady-state serum concentration is reached and is maintained during subsequent applications of a patch of the same size (*see* Figure 1). Patients reach and maintain a steady-state serum concentration that is determined by individual variation in skin permeability and body clearance of fentanyl.

After system removal, serum fentanyl concentrations decline gradually, falling about 50% in approximately 20 to 27 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.

A clinical pharmacology study conducted in healthy adult subjects has shown that the application of heat over the fentanyl transdermal system increased mean overall fentanyl exposure by 120% and average maximum fentanyl level by 61%.

Table 7. Fentanyl Pharmacokinetic Parameters Following First 72-Hour Application of Fentanyl Transdermal System

	Mean (SD) Time to Maximal Concentration T_{max} (hr)	Mean (SD) Maximal Concentration C_{max} (ng/mL)

Fentanyl Transdermal System 12 mcg/hr	28.8 (13.7)	0.38 (0.13)*
Fentanyl Transdermal System 25 mcg/hr	31.7 (16.5)	0.85 (0.26)†
Fentanyl Transdermal System 50 mcg/hr	32.8 (15.6)	1.72 (0.53)†
Fentanyl Transdermal System 75 mcg/hr	35.8 (14.1)	2.32 (0.86)†
Fentanyl Transdermal System 100 mcg/hr	29.9 (13.3)	3.36 (1.28)†

* C_{max} values dose normalized from 4 x 12.5 mcg/hr: Study 2003-038 in healthy volunteers
† C_{max} values: Study C-2002-048 dose proportionality study in healthy volunteers

NOTE: After system removal there is continued systemic absorption from residual fentanyl in the skin so that serum concentrations fall 50%, on average, in approximately 20 to 27 hours.

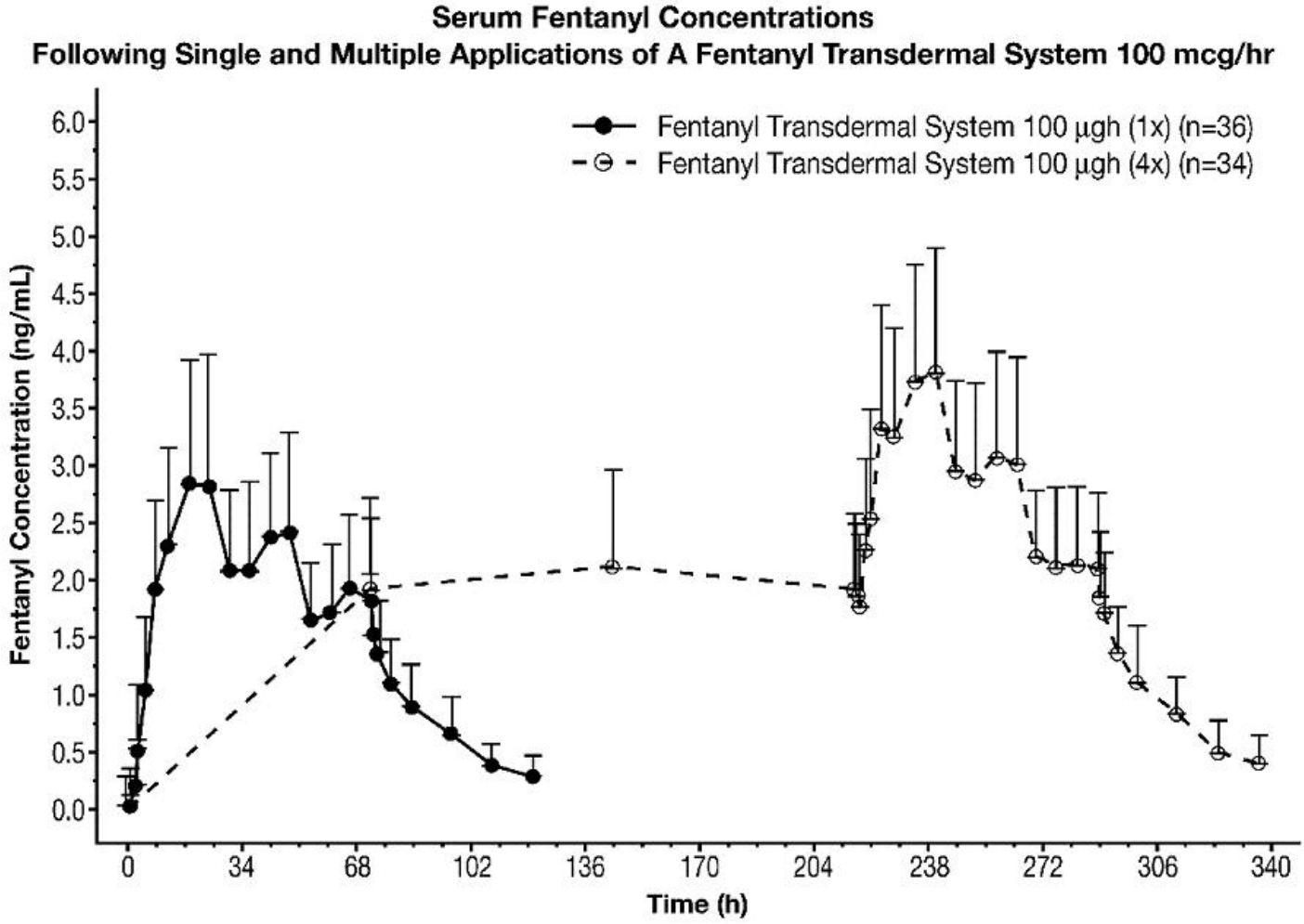


Table 8. Range of Pharmacokinetic Parameters of Intravenous Fentanyl in Patients

	Clearance (L/hr)	Volume of Distribution V_{ss}	Half-Life $t_{1/2}$

	(L/hr) Range [70 kg]	V_{SS} (L/kg) Range	$t_{1/2}$ (hr) Range
Surgical Patients	27-75	3-8	3-12
Hepatically Impaired Patients	3-80*	0.8-8*	4-12*
Renally Impaired Patients	30-78	–	–

* Estimated

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

Distribution

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).

Elimination

Metabolism

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.

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.

Excretion

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%.

Specific Populations

Age: Geriatric Population

Data from intravenous studies with fentanyl suggest that the elderly patients may have reduced clearance and a prolonged half-life. Moreover elderly patients may be more sensitive to the active substance than younger patients. A study conducted with the fentanyl transdermal system in elderly patients demonstrated that fentanyl pharmacokinetics did not differ significantly from young adult subjects, although peak serum concentrations tended to be lower and mean half-life values were prolonged to approximately 34 hours. In this study, a single fentanyl transdermal system 100 mcg/hour patch was applied to a skin site on the upper outer arm in a group of healthy elderly Caucasians ≥65 years old (n=21, mean age 71 years) and worn for 72 hours. The mean C_{max} and AUC_{∞} values were approximately 8% lower and 7% higher, respectively, in the elderly subjects as compared with subjects 18 to 45 years old. Inter-subject variability in AUC_{∞} was higher in elderly subjects than in healthy adult subjects 18 to 45 years (58% and 37%, respectively). The mean half-life value was longer in subjects

≥65 years old than in subjects 18 to 45 years old (34.4 hours versus 23.5 hours) *[see Warnings and Precautions (5.12), Use in Specific Populations (8.5)]*.

Age: Pediatric Population

In 1.5 to 5 year old, non-opioid-tolerant pediatric patients, the fentanyl plasma concentrations were approximately twice as high as that of adult patients. In older pediatric patients, the pharmacokinetic parameters were similar to that of adults. However, these findings have been taken into consideration in determining the dosing recommendations for opioid-tolerant pediatric patients (2 years of age and older). For pediatric dosing information, refer to *[see Dosage and Administration (2.3)]*.

Hepatic Impairment

Information on the effect of hepatic impairment on the pharmacokinetics of fentanyl transdermal system is limited. The pharmacokinetics of fentanyl transdermal system delivering 50 mcg/hour of fentanyl for 72 hours was evaluated in patients hospitalized for surgery. Compared to the controlled patients (n=8), C_{max} and AUC in the patients with cirrhosis (n=9) increased 35% and 73%, respectively.

Because there is *in-vitro* and *in-vivo* evidence of extensive hepatic contribution to the elimination of fentanyl transdermal system, hepatic impairment would be expected to have significant effects on the pharmacokinetics of fentanyl transdermal system. Avoid use of fentanyl transdermal system in patients with severe hepatic impairment *[see Dosage and Administration (2.5), Warnings and Precautions (5.17) and Use in Specific Populations (8.6)]*.

Renal Impairment

Information on the effect of renal impairment on the pharmacokinetics of fentanyl transdermal system is limited. The pharmacokinetics of intravenous injection of 25 mcg/kg fentanyl was evaluated in patients (n=8) undergoing kidney transplantation. An inverse relationship between blood urea nitrogen level and fentanyl clearance was found.

Because there is *in-vivo* evidence of renal contribution to the elimination of fentanyl transdermal system, renal impairment would be expected to have significant effects on the pharmacokinetics of fentanyl transdermal system. Avoid the use of fentanyl transdermal system in patients with severe renal impairment *[see Dosage and Administration (2.6), Warnings and Precautions (5.18) and Use in Specific Populations (8.7)]*.

Drug Interaction Studies

CYP3A4 Inhibitors

Fentanyl is metabolized mainly via the human cytochrome P450 3A4 isoenzyme system (CYP3A4). The interaction between ritonavir, a CYP3A4 inhibitor, and fentanyl was investigated in eleven healthy volunteers in a randomized crossover study. Subjects received oral ritonavir or placebo for 3 days. The ritonavir dose was 200 mg three times a day on Day 1 and 300 mg three times a day on Day 2 followed by one morning dose of 300 mg on Day 3. On Day 2, fentanyl was given as a single IV dose at 5 mcg/kg two hours after the afternoon dose of oral ritonavir or placebo. Naloxone was administered to counteract the side effects of fentanyl. The results suggested that ritonavir might decrease the clearance of fentanyl by 67%, resulting in a 174% (range 52% to 420%) increase in fentanyl $AUC_{0\text{-}\infty}$. The concomitant use of transdermal fentanyl with all CYP3A4 inhibitors (such as ritonavir, ketoconazole, itraconazole, troleandomycin, clarithromycin, nelfinavir, nefazodone, amiodarone, amprenavir, aprepitant, diltiazem, erythromycin, fluconazole, fosamprenavir, verapamil, or grapefruit juice) may result in

an increase in fentanyl plasma concentrations, which could increase or prolong adverse drug effects and may cause potentially fatal respiratory depression. Carefully monitor patients receiving fentanyl transdermal system and any CYP3A4 inhibitor for signs of respiratory depression for an extended period of time and adjust the dosage if warranted *[see Boxed Warning, Warnings and Precautions (5.7) and Drug Interactions (7)]*.

CYP3A4 Inducers
Co-administration with agents that induce CYP3A4 activity may reduce the efficacy of fentanyl transdermal system.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, and Impairment of Fertility

Carcinogenesis
In a two-year carcinogenicity study conducted in rats, fentanyl was not associated with an increased incidence of tumors at subcutaneous doses up to 33 mcg/kg/day in males or
100 mcg/kg/day in females (0.16 and 0.39 times the human daily exposure obtained via the 100 mcg/hr patch based on $AUC_{0\text{-}24h}$ comparison).

Mutagenesis
There was no evidence of mutagenicity in the Ames Salmonella mutagenicity assay, the primary rat hepatocyte unscheduled DNA synthesis assay, the BALB/c 3T3 transformation test, and the human lymphocyte and CHO chromosomal aberration *in-vitro* assays.

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

14 CLINICAL STUDIES

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.

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.

In the pediatric population, the safety of fentanyl transdermal system has been evaluated in 289 patients with chronic pain 2 to 18 years of age. The duration of fentanyl transdermal system use 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.

16 HOW SUPPLIED/STORAGE AND HANDLING

Fentanyl transdermal system is supplied in cartons containing 5 individual child-resistant 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-12*	3.9	1.375	0406-9112-76
Fentanyl transdermal system-25	7.8	2.75	0406-9125-76
Fentanyl transdermal system-37.5	11.7	4.125	0406-9037-76
Fentanyl transdermal system-50	15.6	5.50	0406-9150-76
Fentanyl transdermal system-62.5	19.6	6.875	0406-9062-76
Fentanyl transdermal system-75	23.4	8.25	0406-9175-76
Fentanyl transdermal system-100	31.3	11.0	0406-9100-76

* This lowest strength is designated as 12 mcg/hr (however, the actual strength is 12.5 mcg/hr) to distinguish it from a 125 mcg/hr strength that could be prescribed by using multiple transdermal systems.

Store in original unopened pouch. Store up to 25°C (77°F); excursions permitted to 15 to 30°C (59 to 86°F) [see USP Controlled Room Temperature].

Store fentanyl transdermal system securely and dispose of properly *[see Patient Counseling Information (17)]*.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).

Storage and Disposal
Because of the risks associated with accidental ingestion, misuse, and abuse, advise patients to store fentanyl transdermal system securely, out of sight and reach of children, and in a location not accessible by others, including visitors to the home. Inform patients that leaving fentanyl transdermal system unsecured can pose a deadly risk to others in the home *[see Warnings and Precautions (5.1, 5.3), Drug Abuse and Dependence (9.2)]*.

Advise patients and caregivers that when medicines are no longer needed, they should be disposed of promptly. Expired, unwanted, or unused fentanyl transdermal system should be disposed of by folding the patch so that the adhesive side of the patch adheres to itself, and immediately flushing down the toilet (if a drug take-back option is not readily available) *[see Instructions for Use]*. Inform patients that they can visit www.fda.gov/drugdisposal for a complete list of medicines recommended for disposal by flushing, as well as additional information on disposal of unused medicines.

Addiction, Abuse, and Misuse
Inform patients that the use of fentanyl transdermal system, even when taken as recommended, can result in addiction, abuse, and misuse, which can lead to overdose and death *[see Warnings and Precautions (5.1)]*. Instruct patients not to share fentanyl transdermal system with others and to take steps to protect fentanyl transdermal system from theft or misuse.

Life-Threatening Respiratory Depression
Inform patients of the risk of life-threatening respiratory depression, including information that the risk is greatest when starting fentanyl transdermal system or when the dosage is increased, and that it can occur even at recommended dosages.

Educate patients and caregivers on how to recognize respiratory depression and emphasize the importance of calling 911 or getting emergency medical help right away in the event of a known or suspected overdose *[see Warnings and Precautions (5.2)].*

Accidental Exposure
Inform patients that accidental exposure, especially in children, may result in respiratory depression or death *[see Warnings and Precautions (5.3)]*.

Fentanyl transdermal system can be accidentally transferred to children. Instruct patients to take special precautions to avoid accidental contact when holding or caring for children.

Instruct patients that, if the patch dislodges and accidentally sticks to the skin of another person, to immediately take the patch off, wash the exposed area with water and seek medical attention for the accidentally exposed individual as accidental exposure may lead to death or other serious medical problems.

Interactions with Benzodiazepines and Other CNS Depressants
Inform patients and caregivers that potentially fatal additive effects may occur if fentanyl transdermal system is used with benzodiazepines or other CNS depressants, including alcohol (e.g., non-benzodiazepine sedative/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, gabapentinoids [gabapentin or pregabalin], and other opioids), and not to use these concomitantly unless supervised

by a healthcare provider *[see Warnings and Precautions (5.4), Drug Interactions (7)].*

Patient Access to an Opioid Overdose Reversal Agent for the Emergency Treatment of Opioid Overdose

Inform patients and caregivers about opioid overdose reversal agents (e.g., naloxone, nalmefene). Discuss the importance of having access to an opioid overdose reversal agent, especially if the patient has risk factors for overdose (e.g., concomitant use of CNS depressants, a history of opioid use disorder, or prior opioid overdose) or if there are household members (including children) or other close contacts at risk for accidental ingestion or opioid overdose.

Discuss with the patient the options for obtaining an opioid overdose reversal agent (e.g., prescription, over-the-counter, or as part of a community-based program) *[see Dosage and Administration (2.2), Warnings and Precautions (5.4)]*.

Educate patients and caregivers on how to recognize the signs and symptoms of an overdose.

Explain to patients and caregivers that effects of opioid overdose reversal agents like naloxone and nalmefene are temporary, and that they must call 911 or get emergency medical help right away in all cases of known or suspected opioid overdose, even if an opioid overdose reversal agent is administered *[see Overdosage (10)]*.

Advise patients and caregivers:

- how to treat with the overdose reversal agent in the event of an opioid overdose.
- to tell family and friends about the opioid overdose reversal agent, and to keep it in a place where family and friends can access it in an emergency.
- to read the Patient Information (or other educational material) that will come with their opioid overdose reversal agent. Emphasize the importance of doing this before an opioid emergency happens, so the patient and caregiver will know what to do.

Hyperalgesia and Allodynia
Inform patients and caregivers not to increase opioid dosage without first consulting a clinician. Advise patients to seek medical attention if they experience symptoms of hyperalgesia, including worsening pain, increased sensitivity to pain, or new pain *[see Warnings and Precautions (5.10), Adverse Reactions (6.2)].*

Serotonin Syndrome
Inform patients that opioids could cause a rare but potentially life-threatening condition resulting from concomitant administration of serotonergic drugs. Warn patients of the symptoms and signs of serotonin syndrome, and to seek medical attention right away if symptoms develop. Instruct patients to inform their healthcare providers if they are taking, or plan to take serotonergic medications *[see Warnings and Precautions (5.11), Drug Interactions (7)]*.

MAOI Interaction
Inform patients to avoid taking fentanyl transdermal system while using any drugs that inhibit monoamine oxidase. Patients should not start MAOIs while taking fentanyl transdermal system *[see Drug Interactions (7)]*.

Important Administration Instructions
Advise patients never to change the dose of fentanyl transdermal system or the number of patches applied to the skin unless instructed to do so by the prescribing healthcare

professional.

Warnings About Heat
Warn patients of the potential for temperature-dependent increases in fentanyl release from the patch that could result in an overdose of fentanyl. Instruct patients to contact their healthcare provider if they develop a high fever. Instruct patients to:

- avoid strenuous exertion that can increase body temperature while wearing the patch
- avoid exposing the fentanyl transdermal system application site and surrounding area to direct external heat sources including heating pads, electric blankets, sunbathing, heat or tanning lamps, saunas, hot tubs or hot baths, and heated waterbeds.

Important Discontinuation Instructions
In order to avoid developing withdrawal symptoms, instruct patients not to discontinue fentanyl transdermal system without first discussing a tapering plan with the prescriber *[see Dosage and Administration (2.9)]*.

Driving or Operating Heavy Machinery
Inform patients that fentanyl transdermal system may impair the ability to perform potentially hazardous activities such as driving a car or operating heavy machinery. Advise patients not to perform such tasks until they know how they will react to the medication *[see Warnings and Precautions (5.22)]*.

Constipation
Advise patients of the potential for severe constipation, including management instructions and when to seek medical attention *[see Adverse Reactions (6), Clinical Pharmacology (12.2)]*.

Adrenal Insufficiency
Inform patients that opioids could cause adrenal insufficiency, a potentially life-threatening condition. Adrenal insufficiency may present with non-specific symptoms and signs such as nausea, vomiting, anorexia, fatigue, weakness, dizziness, and low blood pressure. Advise patients to seek medical attention if they experience a constellation of these symptoms *[see Warnings and Precautions (5.13)]*.

Hypotension
Inform patients that fentanyl transdermal system may cause orthostatic hypotension and syncope. Instruct patients how to recognize symptoms of low blood pressure and how to reduce the risk of serious consequences should hypotension occur (e.g., sit or lie down, carefully rise from a sitting or lying position) *[see Warnings and Precautions (5.14)]*.

Anaphylaxis
Inform patients that anaphylaxis, including anaphylactic shock, has been reported with ingredients contained in fentanyl transdermal system. Advise patients how to recognize such a reaction and when to seek medical attention *[see Contraindications (4), Adverse Reactions (6)]*.

Pregnancy
Neonatal Opioid Withdrawal Syndrome
Inform female patients of reproductive potential that use of fentanyl transdermal system for an extended period of time during pregnancy can result in neonatal opioid withdrawal

syndrome, which may be life-threatening if not recognized and treated *[see Warnings and Precautions (5.5), Use in Specific Populations (8.1)]*.

Embryo-Fetal Toxicity
Inform female patients of reproductive potential that fentanyl transdermal system can cause fetal harm and to inform their healthcare provider of known or suspected pregnancy *[see Use in Specific Populations (8.1)]*.

Lactation
Advise patients that breastfeeding is not recommended during treatment with fentanyl transdermal system *[see Use in Specific Populations (8.2)]*.

Infertility
Inform patients that use of opioids for an extended period of time may cause reduced fertility. It is not known whether these effects on fertility are reversible *[see Use in Specific Populations (8.3)]*.

Revised: 01/2026

An electronic copy of this medication guide can be obtained from www.mallinckrodt.com/Medguide/X30000067.pdf or by calling 1-800-778-7898 for alternate delivery options.

Medication Guide
Fentanyl Transdermal System, CII
(fĕn´ tə-nĭl)

Fentanyl transdermal system is:

- A strong prescription pain medicine that contains an opioid (narcotic) that is used to manage severe and persistent pain that requires an extended treatment period with a daily opioid pain medicine, in people who are already regularly using opioid pain medicine when other pain medicines do not treat your pain well enough or you cannot tolerate them.
- A long-acting (extended-release) opioid pain medicine that can put you at risk for overdose and death. Even if you take your dose correctly as prescribed you are at risk for opioid addiction, abuse, and misuse that can lead to death.
- Not to be used on an “as needed” basis.

Important information about fentanyl transdermal system:

- **Get emergency help or call 911 right away if you use too much fentanyl transdermal system (overdose).** When you first start taking fentanyl transdermal system, when your dose is changed, or if you take too much (overdose), serious or life-threatening breathing problems that can lead to death may occur. Ask your healthcare provider about medicines like naloxone or nalmefene that can be used in an emergency to reverse an opioid overdose.
- Taking fentanyl transdermal system with other opioid

medicines, benzodiazepines, gabapentinoids (gabapentin or pregabalin), alcohol, or other central nervous system depressants (including street drugs) may cause severe drowsiness, decreased awareness, breathing difficulties, with slow or shallow breathing, coma, and death.
- Never give anyone else your fentanyl transdermal system. They could die from taking it. Selling or giving away fentanyl transdermal system is against the law.
- Store fentanyl transdermal system, securely, out of sight and reach of children, and in a location not accessible by others, including visitors to the home.
- If the patch accidentally sticks to a family member while in close contact, take the patch off, wash the area with water, and get emergency help right away because an accidental exposure to fentanyl transdermal system can lead to death or other serious medical problems.
- Dispose of expired, unwanted, or unused fentanyl transdermal system, by folding the patch so that the adhesive side of the patch adheres to itself, and immediately flushing down the toilet (if a drug take-back option is not readily available) *[see Instructions for Use]*. Visit www.fda.gov/drugdisposal for additional information on disposal of unused medicines.

Do not use fentanyl transdermal system if you have:
- severe asthma, trouble breathing, or other lung problems.
- a bowel blockage or have narrowing of the stomach or intestines.

Before applying fentanyl transdermal system, tell your healthcare provider if you have a history of:
- head injury, seizures
- problems urinating
- abuse of street or prescription drugs, alcohol addiction, opioid overdose, or mental health problems.
- liver, kidney, thyroid problems
- pancreas or gallbladder problems

Tell your healthcare provider if you:
- notice your pain getting worse. If your pain gets worse after you use fentanyl transdermal system, do not use more of fentanyl transdermal system without first talking to your healthcare provider. Talk to your healthcare provider if the pain that you have increases, if you feel more sensitive to pain, or if you have new pain after using fentanyl transdermal system.
- have a fever
- **are pregnant or planning to become pregnant.** Use of fentanyl transdermal system for an extended period of time during pregnancy can cause withdrawal symptoms in

your newborn baby that could be life-threatening if not recognized and treated.
- **are breastfeeding.** Not recommended during treatment with fentanyl transdermal system. It may harm your baby.
- are living in a household where there are small children or someone who has abused street or prescription drugs.
- are taking prescription or over-the-counter medicines, vitamins, or herbal supplements. Taking fentanyl transdermal system with certain other medicines can cause serious side effects that could lead to death.

When using fentanyl transdermal system:
- Do not change your dose. Apply fentanyl transdermal system exactly as prescribed by your healthcare provider. Use the lowest dose possible for the shortest time needed.
- See the detailed Instructions for Use for information about how to apply and dispose of the fentanyl transdermal system. Visit www.fda.gov/drugdisposal for additional information on disposal of unused medicines.
- Do not apply more than 1 patch at the same time unless your healthcare provider tells you to.
- You should wear the fentanyl transdermal system continuously for 3 days, unless advised otherwise by your healthcare provider.
- Do not cut, break, chew, crush, dissolve, snort, or inject fentanyl transdermal system because this may cause you to overdose and die.
- **Call your healthcare provider if the dose you are using does not control your pain.**
- **Do not stop using fentanyl transdermal system without talking to your healthcare provider.**

While using fentanyl transdermal system DO NOT:
- Take hot baths or sunbathe, use hot tubs, saunas, heating pads, electric blankets, heated waterbeds, or tanning lamps, or engage in exercise that increases your body temperature. These can cause an overdose that can lead to death.
- Drive or operate heavy machinery, until you know how fentanyl transdermal system affects you. Fentanyl transdermal system can make you sleepy, dizzy, or lightheaded.
- Drink alcohol or use prescription or over-the-counter medicines that contain alcohol. Using products containing alcohol during treatment with fentanyl transdermal system may cause you to overdose and die.

The possible side effects of fentanyl transdermal system are:

- constipation, nausea, sleepiness, vomiting, tiredness, headache, dizziness, abdominal pain, itching, redness, or rash where the patch is applied. Call your healthcare provider if you have any of these symptoms and they are severe.

Get emergency medical help or call 911 right away if you have:

- trouble breathing, shortness of breath, fast heartbeat, chest pain, swelling of your face, tongue or throat, extreme drowsiness, light-headedness when changing positions, feeling faint, agitation, high body temperature, trouble walking, stiff muscles, or mental changes such as confusion.

These are not all the possible side effects of fentanyl transdermal system. Call your healthcare provider for medical advice about side effects. You may report side effects to FDA at
1-800-FDA-1088. **For more information go to dailymed.nlm.nih.gov**
Manufactured by: LTS Lohmann Therapy Systems, Corp., W. Caldwell, NJ 07006
Manufactured for: SpecGx LLC, Webster Groves, MO 63119 USA, www.mallinckrodt.com or call 1-800-778-7898
X30000067
Mallinckrodt™
Pharmaceuticals

This Medication Guide has been approved by the U.S. Food and Drug Administration.
Revised: 01/2026

Instructions for Use
Fentanyl Transdermal System CII

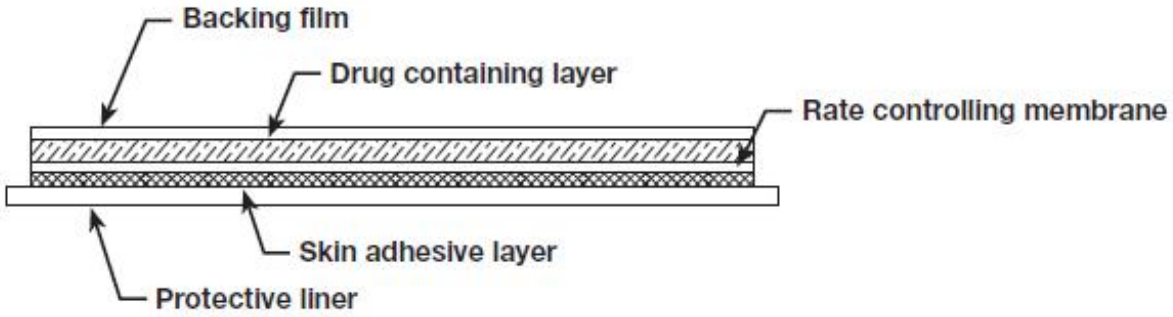
Be sure that you read, understand, and follow these Instructions for Use before you apply fentanyl transdermal system. Talk to your healthcare provider or pharmacist if you have any questions.

Important information about the fentanyl transdermal system appearance:

- **Fentanyl transdermal systems are a rectangular, opaque patch with rounded corners.**
- **Fentanyl transdermal system comes in 7 different dosage strengths and sizes:**
  - **12 mcg/hr: Fentanyl Transdermal System 12 mcg/hr printed in green**
  - **25 mcg/hr: Fentanyl Transdermal System 25 mcg/hr printed in green**
  - **37.5 mcg/hr: Fentanyl Transdermal System 37.5 mcg/hr printed in green**
  - **50 mcg/hr: Fentanyl Transdermal System 50 mcg/hr printed in green**
  - **62.5 mcg/hr: Fentanyl Transdermal System 62.5 mcg/hr printed in**

green
  - **75 mcg/hr: Fentanyl Transdermal System 75 mcg/hr printed in green**
  - **100 mcg/hr: Fentanyl Transdermal System 100 mcg/hr printed in green**
- **The 12 mcg/hour system has a green border.**
- **The 25, 37.5, 50, 62.5, 75 and 100 mcg/hour systems have green stripes that increase in number with each sequential increasing dosage strength.**

Parts of the fentanyl transdermal system:



Before applying fentanyl transdermal system

- **Each fentanyl transdermal system is sealed in its own protective pouch. Do not remove a fentanyl transdermal system from the pouch until you are ready to use it.**
- **Do not use a fentanyl transdermal system if the pouch seal is broken or the patch is cut, damaged or changed in any way.**
- **Fentanyl transdermal systems are available in 7 different dosage strengths and patch sizes. Make sure you have the right dose patch or patches that have been prescribed for you.**

<u>Applying a fentanyl transdermal system</u>
<u>1. Skin areas where the fentanyl transdermal system may be applied:</u>
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 (*see* Figures 1-4).

For children (and adults with mental impairment):

- **Put the patch on the upper back** (*see* Figure 2)**.** This will lower the chances that the child will remove the patch and put it in their mouth.

For adults and children:

- <u>Do not</u> put a fentanyl transdermal system on skin that is very oily, burned, broken out, cut, irritated, or damaged in any way.
- 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 (*see* Figure 5).
- **Talk to your healthcare provider if you have questions about skin application sites.**

2. Prepare to apply a fentanyl transdermal system:
- Choose the time of day that is best for you to apply fentanyl transdermal system. Change it at about the same time of day (3 days or 72 hours after you apply the patch) or as directed by your healthcare provider.
- Do not wear more than one fentanyl transdermal system at a time unless your healthcare provider tells you to do so. Before applying a new fentanyl transdermal system, remove the patch you have been wearing.
- Clean the skin area with clear water **only**. **Pat skin completely dry.** Do not use anything on the skin such as soaps, lotions, oils, or alcohol before the patch is applied.

3. Open the pouch: Fold and tear at slit, or cut at line taking care not to cut the patch. Remove the fentanyl transdermal system. Each fentanyl transdermal system is sealed in its own protective pouch. Do not remove the fentanyl transdermal system from the pouch until you are ready to use it (*see* Figure 6).

4. Peel: Peel off both parts of the protective liner from the patch. Each fentanyl transdermal system has a clear plastic backing that can be peeled off in two pieces

backing that can be peeled off in two pieces. This covers the sticky side of the patch. Carefully peel this backing off. Throw the clear plastic backing away. **Touch the sticky side of the fentanyl transdermal system as little as possible** (*see* Figure 7)**.**

Figure 1

Figure 2

Figure 3

Figure 4

Figure 5

Figure 6

Figure 7

Figure 8

Figure 9

Figure 10

5. Press: Press the patch onto the chosen skin site **with the palm of your hand and hold there for at least 30 seconds** (*see* Figure 8). Make sure it sticks well, especially at the edges.

- Fentanyl transdermal system may not stick to all people. You need to check the patch often to make sure that it is sticking well to the skin.
- If the patch falls off right away after applying, throw it away and put a new one on at a different skin site. See the section below called "Disposing of a fentanyl transdermal system".
- If you have a problem with the patch not sticking
  - Apply first aid tape only to the edges of the patch.
  - If you continue to have problems with the patch not sticking, you may cover the patch with a transparent adhesive film dressing such as Bioclusive™ or Tegaderm™. These are special see-through adhesive dressings. **Never cover a fentanyl transdermal system with any other bandage or tape.** Remove the backing from the Bioclusive™ or Tegaderm™ dressing and place it carefully over the fentanyl transdermal system, smoothing it over the patch and your skin.
- **If your patch falls off before 3 days (72 hours) of use, dispose of (throw away) properly. See the section below "Disposing of a fentanyl transdermal system". Apply a new fentanyl transdermal system on at a different skin site. Be sure to let your healthcare provider know that this has happened, and do not replace the new patch until 3 days (72 hours) after you put it on (or as**

directed by your healthcare provider).

6. Wash your hands when you have finished applying a fentanyl transdermal system.
7. Remove a fentanyl transdermal system after wearing it for 3 days (72 hours). **Dispose of the used patch right away. See the section below "Disposing of a fentanyl transdermal system".** Choose a **different** skin site to apply a new fentanyl transdermal system. Repeat Steps 2 through 6 above when applying a new fentanyl transdermal system.
Do not apply the new patch to the same place as the last one.
Water and fentanyl transdermal system

- You can bathe, swim or shower while you are wearing a fentanyl transdermal system. If the patch falls off before 3 days (72 hours) after application, dispose of properly. See the section below "Disposing of a fentanyl transdermal system". Apply a new fentanyl transdermal system on at a different skin site. Be sure to let your healthcare provider know that this has happened, and do not replace the new patch until 3 days (72 hours) after you put it on (or as directed by your healthcare provider).

Disposing of a fentanyl transdermal system

- Fold the used fentanyl transdermal system in half so that the sticky side sticks to itself (*see* Figure 9). **Flush the used fentanyl transdermal system down the toilet right away** (*see* Figure 10). **A used fentanyl transdermal system can be very dangerous for or lead to death in babies, children, pets, and adults who have not been prescribed fentanyl transdermal system.**
- Throw away any fentanyl transdermal systems 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 trash can.

This Instructions for Use has been approved by the U.S. Food and Drug Administration.

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Rx only

Manufactured by:
LTS Lohmann Therapy Systems, Corp.
W. Caldwell, NJ 07006

Manufactured for:
SpecGx LLC
Webster Groves, MO 63119 USA

Printed in USA

6520730

Issued: 01/2026

Mallinckrodt™
Pharmaceuticals

PRINCIPAL DISPLAY PANEL - 12 mcg/hr

NDC 0406-9112-76
Five (12 mcg/hr) **Systems**
FENTANYL TRANSDERMAL SYSTEM
12 mcg/hr
Rx only
CII

***In vivo* delivery of 12 mcg/hr fentanyl for 72 hours**

Because serious or life-threatening breathing problems could result,
DO NOT USE FENTANYL TRANSDERMAL SYSTEM:

- **For pain that can be treated with immediate-release opioids or non-opioid analgesics**
- **For intermittant (on an as-needed basis) pain**
- **For any postoperative pain**

- **Unless you are opioid tolerant (have been using other narcotic opioid medicines)**

Each transdermal system contains: 1.375 mg fentanyl
DO NOT USE IF SEAL ON POUCH IS BROKEN
KEEP OUT OF REACH OF CHILDREN
Read enclosed fentanyl transdermal system Medication Guide for important safety information.

PHARMACIST: Dispense the Medication Guide provided separately to each patient.

For Opioid-Tolerant Patients Only

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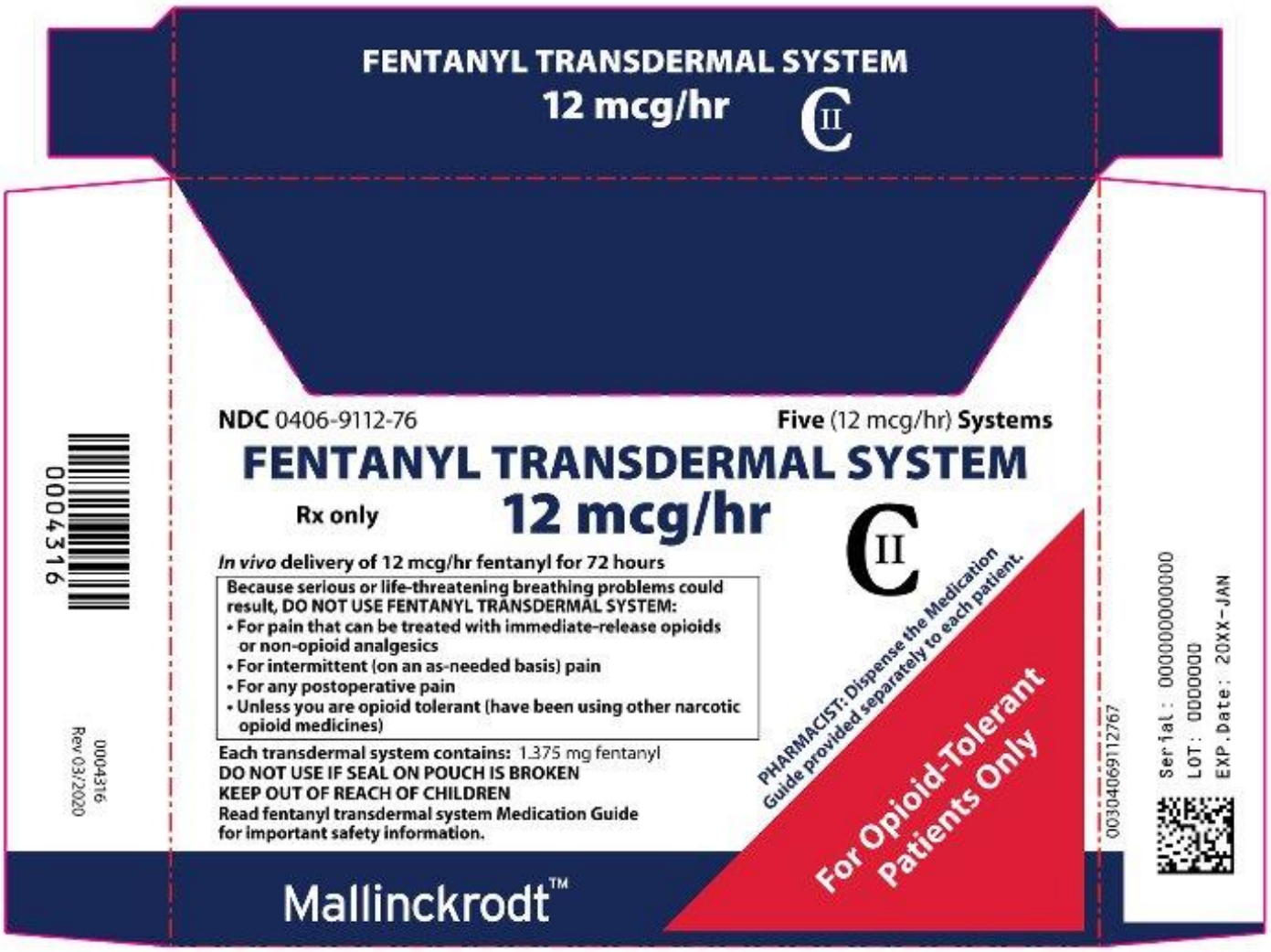

PRINCIPAL DISPLAY PANEL - 25 mcg/hr

NDC 0406-9125-76
Five (25 mcg/hr) **Systems**
FENTANYL TRANSDERMAL SYSTEM
25 mcg/hr
Rx only
CII

***In vivo* delivery of 25 mcg/hr fentanyl for 72 hours**

Because serious or life-threatening breathing problems could result,
DO NOT USE FENTANYL TRANSDERMAL SYSTEM:

- **For pain that can be treated with immediate-release opioids or non-opioid analgesics**
- **For intermittant (on an as-needed basis) pain**
- **For any postoperative pain**
- **Unless you are opioid tolerant (have been using other narcotic opioid medicines)**

Each transdermal system contains: 2.75mg fentanyl
DO NOT USE IF SEAL ON POUCH IS BROKEN
KEEP OUT OF REACH OF CHILDREN
Read enclosed fentanyl transdermal system Medication Guide for important safety information.

PHARMACIST: Dispense the Medication Guide provided separately to each patient.

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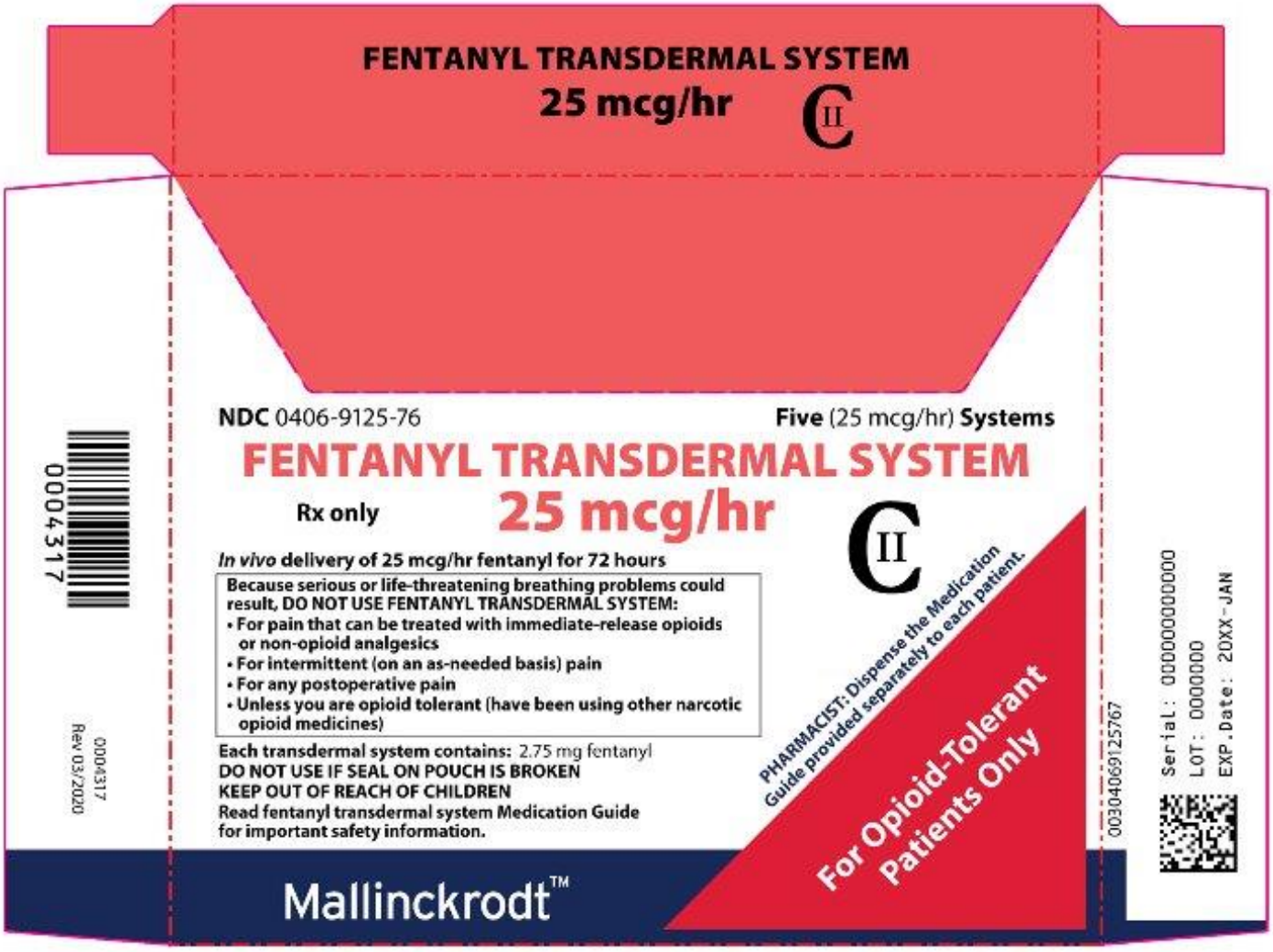

PRINCIPAL DISPLAY PANEL - 37.5 mcg/hr

NDC 0406-9037-76
Five (37.5 mcg/hr) **Systems**

FENTANYL TRANSDERMAL SYSTEM

Rx only
37.5 mcg/hr
CII

In vivo **delivery of 37.5 mcg/hr fentanyl for 72 hours**

Because serious or life-threatening breathing problems could result, DO NOT USE FENTANYL TRANSDERMAL SYSTEM:

- **For pain that can be treated with immediate-release opioids or non-opioid analgesics**
- **For intermittant (on an as-needed basis) pain**
- **For any postoperative pain**
- **Unless you are opioid tolerant (have been using other narcotic opioid medicines)**

Each transdermal system contains: 4.125 mg fentanyl
DO NOT USE IF SEAL ON POUCH IS BROKEN
KEEP OUT OF REACH OF CHILDREN
Read enclosed fentanyl transdermal system Medication Guide for important safety information.

PHARMACIST: Dispense the Medication Guide provided separately to each patient.

For Opioid-Tolerant Patients Only

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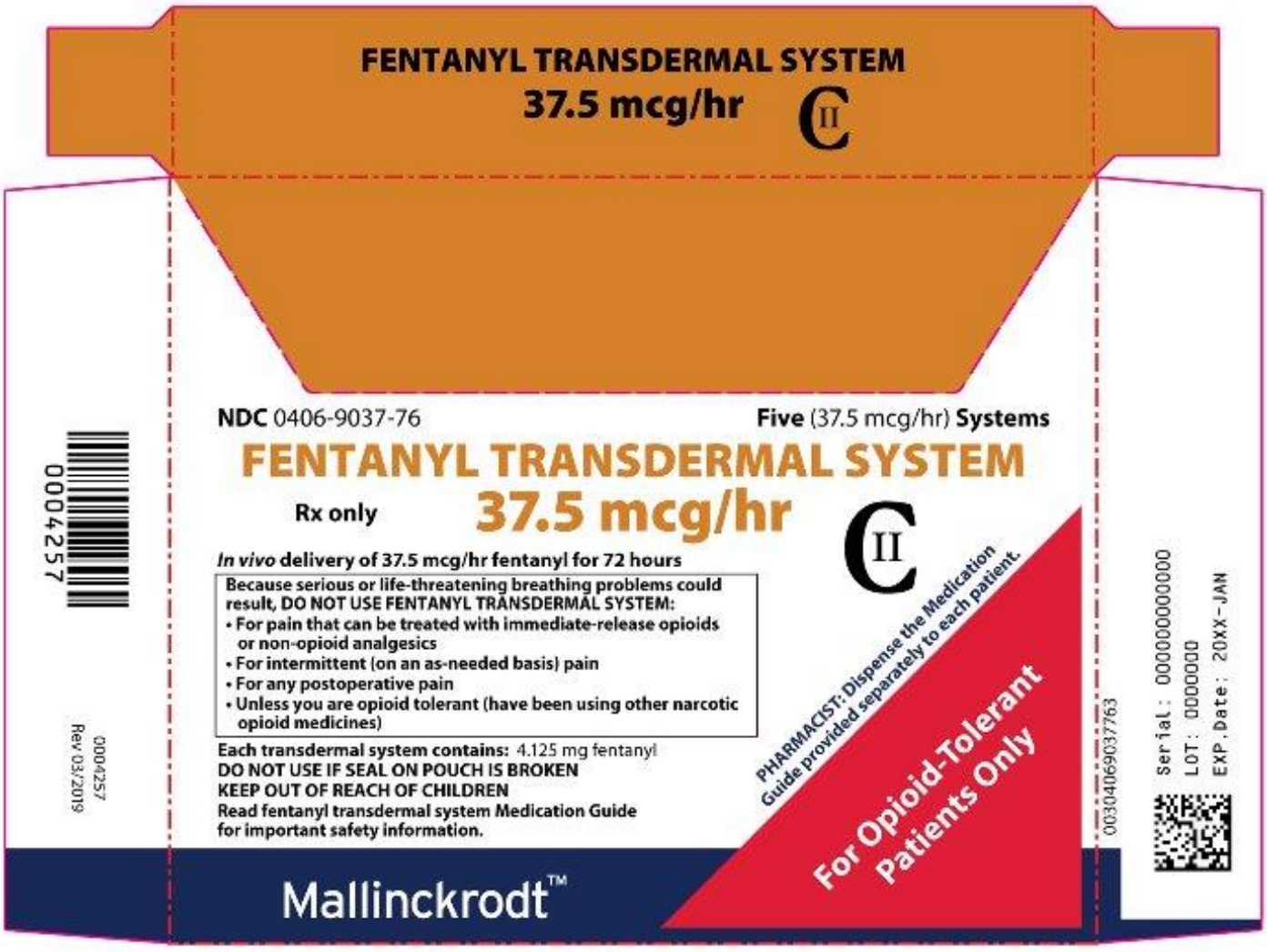

PRINCIPAL DISPLAY PANEL - 50 mcg/hr

NDC 0406-9150-76
Five (50 mcg/hr) **Systems**
FENTANYL TRANSDERMAL SYSTEM

50 mcg/hr
Rx only
CII

***In vivo* delivery of 50 mcg/hr fentanyl for 72 hours**

Because serious or life-threatening breathing problems could result,
DO NOT USE FENTANYL TRANSDERMAL SYSTEM:

- **For pain that can be treated with immediate-release opioids or non-opioid analgesics**
- **For intermittant (on an as-needed basis) pain**
- **For any postoperative pain**
- **Unless you are opioid tolerant (have been using other narcotic opioid medicines)**

Each transdermal system contains: 5.50mg fentanyl

DO NOT USE IF SEAL ON POUCH IS BROKEN
KEEP OUT OF REACH OF CHILDREN
Read enclosed fentanyl transdermal system Medication Guide for important safety information.

PHARMACIST: Dispense the Medication Guide provided separately to each patient.

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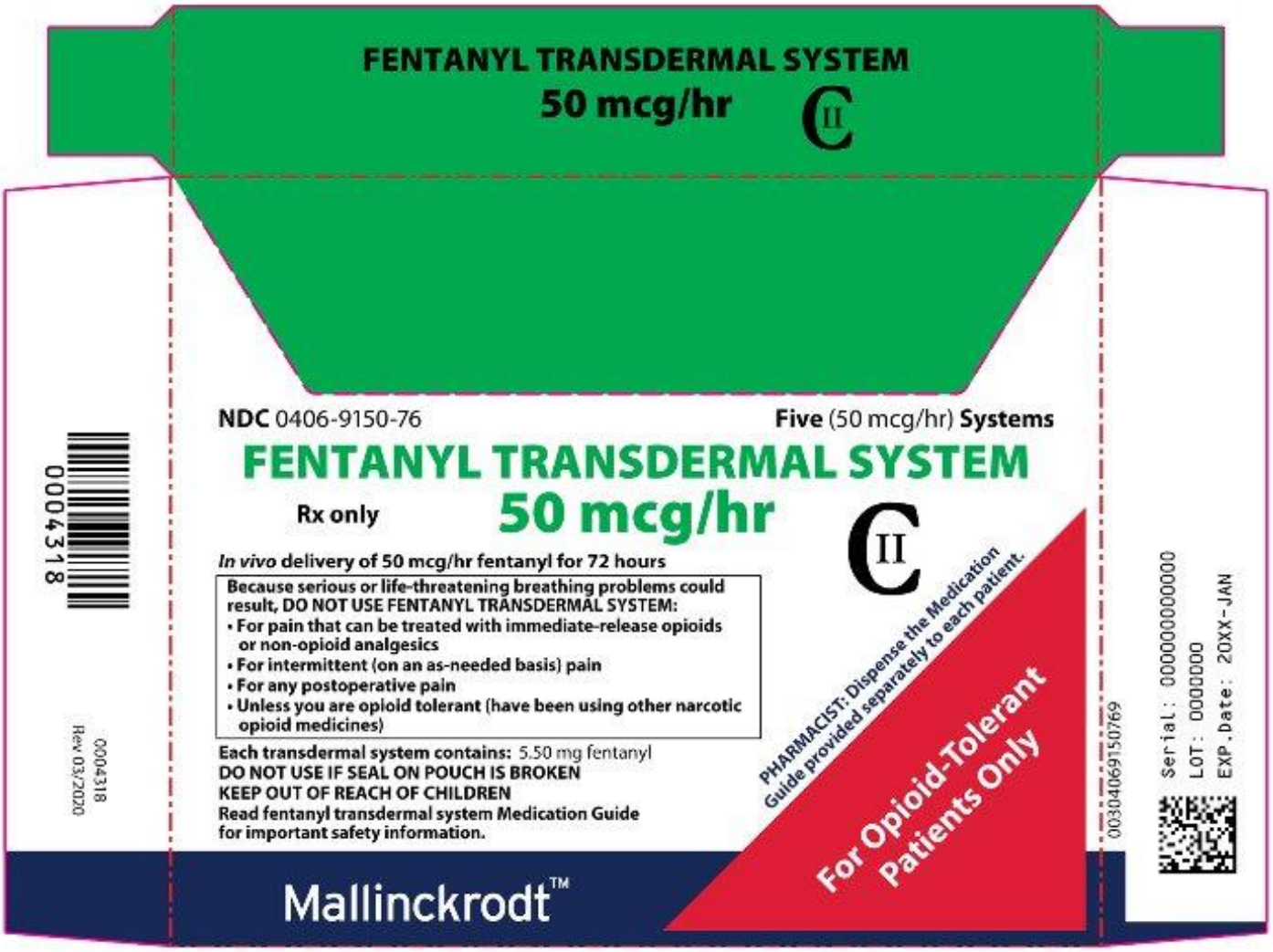

PRINCIPAL DISPLAY PANEL - 62.5 mcg/hr

NDC 0406-9062-76
Five (62.5 mcg/hr) **Systems**

FENTANYL TRANSDERMAL SYSTEM

Rx only
62.5 mcg/hr
CII

***In vivo* delivery of 62.5 mcg/hr fentanyl for 72 hours**

Because serious or life-threatening breathing problems could result, DO NOT USE FENTANYL TRANSDERMAL SYSTEM:

- **For pain that can be treated with immediate-release opioids or non-opioid analgesics**
- **For intermittant (on an as-needed basis) pain**
- **For any postoperative pain**
- **Unless you are opioid tolerant (have been using other narcotic opioid medicines)**

Each transdermal system contains: 6.875 mg fentanyl
DO NOT USE IF SEAL ON POUCH IS BROKEN
KEEP OUT OF REACH OF CHILDREN
Read fentanyl transdermal system Medication Guide for important safety information.

PHARMACIST: Dispense the Medication Guide provided separately to each patient.

For Opioid-Tolerant Patients Only

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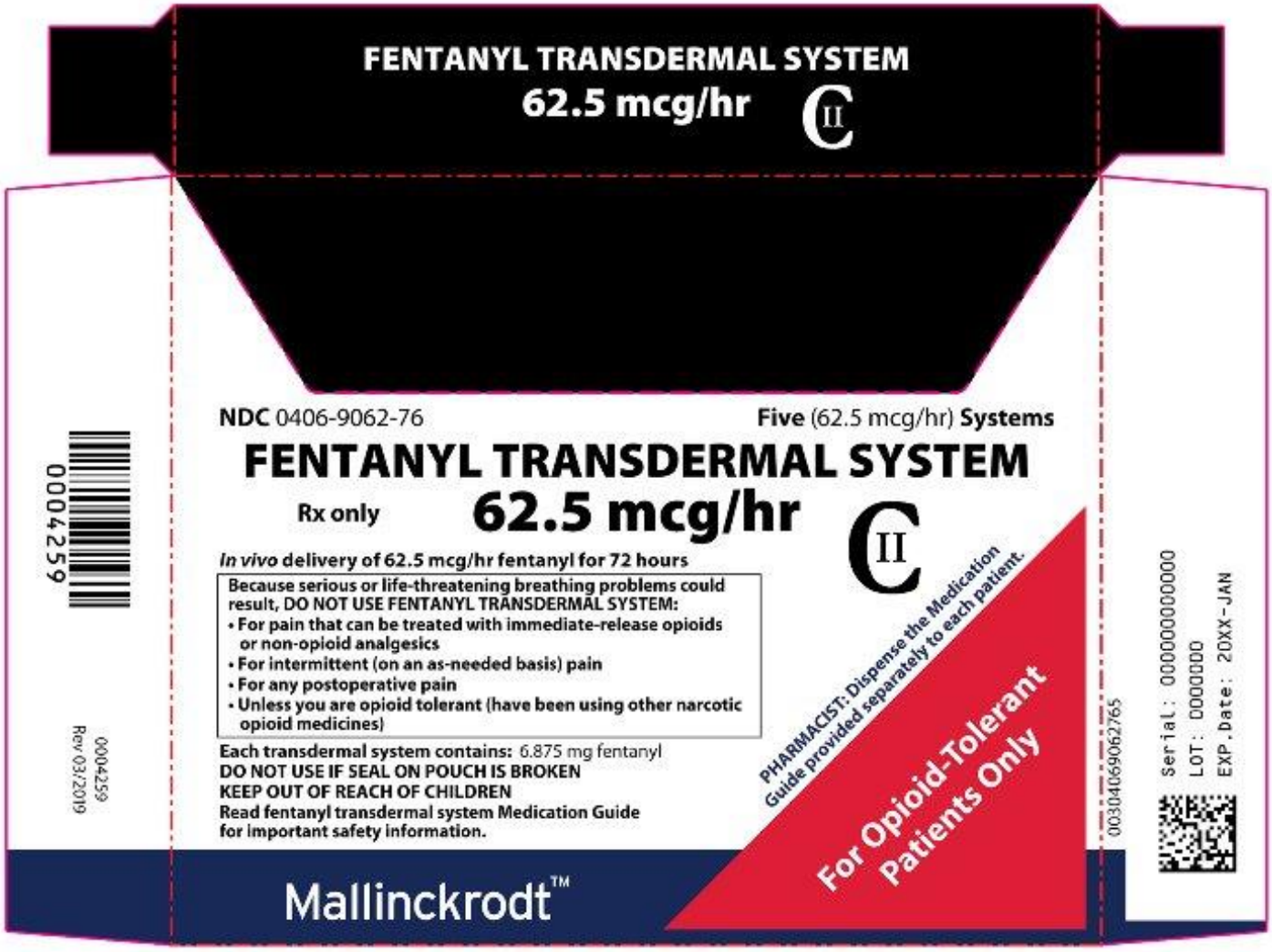

PRINCIPAL DISPLAY PANEL - 75 mcg/hr

NDC 0406-9175-76
Five (75 mcg/hr) **Systems**
FENTANYL TRANSDERMAL SYSTEM

75 mcg/hr
Rx only
CII

***In vivo* delivery of 75 mcg/hr fentanyl for 72 hours**

Because serious or life-threatening breathing problems could result, DO NOT USE FENTANYL TRANSDERMAL SYSTEM:

- **For pain that can be treated with immediate-release opioids or non-opioid analgesics**
- **For intermittant (on an as-needed basis) pain**
- **For any postoperative pain**
- **Unless you are opioid tolerant (have been using other narcotic opioid medicines)**

Each transdermal system contains: 8.25mg fentanyl
DO NOT USE IF SEAL ON POUCH IS BROKEN
KEEP OUT OF REACH OF CHILDREN
Read enclosed fentanyl transdermal system Medication Guide for important safety information.

PHARMACIST: Dispense the Medication Guide provided separately to each patient.

For Opioid-Tolerant Patients Only

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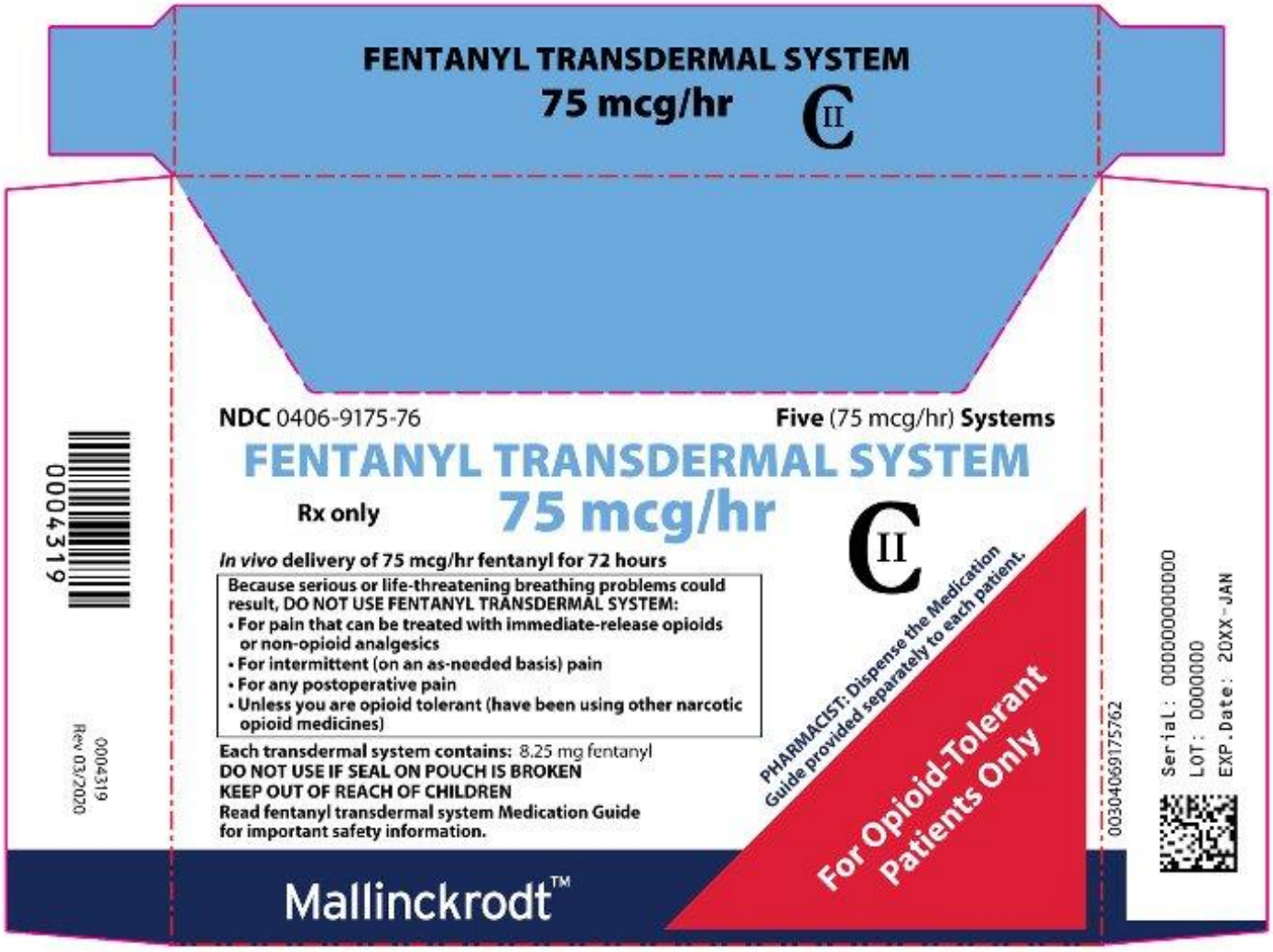

PRINCIPAL DISPLAY PANEL - 100 mcg/hr

NDC 0406-9100-76
Five (100 mcg/hr) **Systems**
FENTANYL TRANSDERMAL SYSTEM
100 mcg/hr
Rx only
CII

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

Because serious or life-threatening breathing problems could result, DO NOT USE FENTANYL TRANSDERMAL SYSTEM:

- **For pain that can be treated with immediate-release opioids or non-opioid analgesics**
- **For intermittant (on an as-needed basis) pain**
- **For any postoperative pain**
- **Unless you are opioid tolerant (have been using other narcotic opioid medicines)**

Each transdermal system contains: 11.0 mg fentanyl
DO NOT USE IF SEAL ON POUCH IS BROKEN
KEEP OUT OF REACH OF CHILDREN
Read enclosed fentanyl transdermal system Medication Guide for important safety information.

PHARMACIST: Dispense the Medication Guide provided separately to each patient.

For Opioid-Tolerant Patients Only

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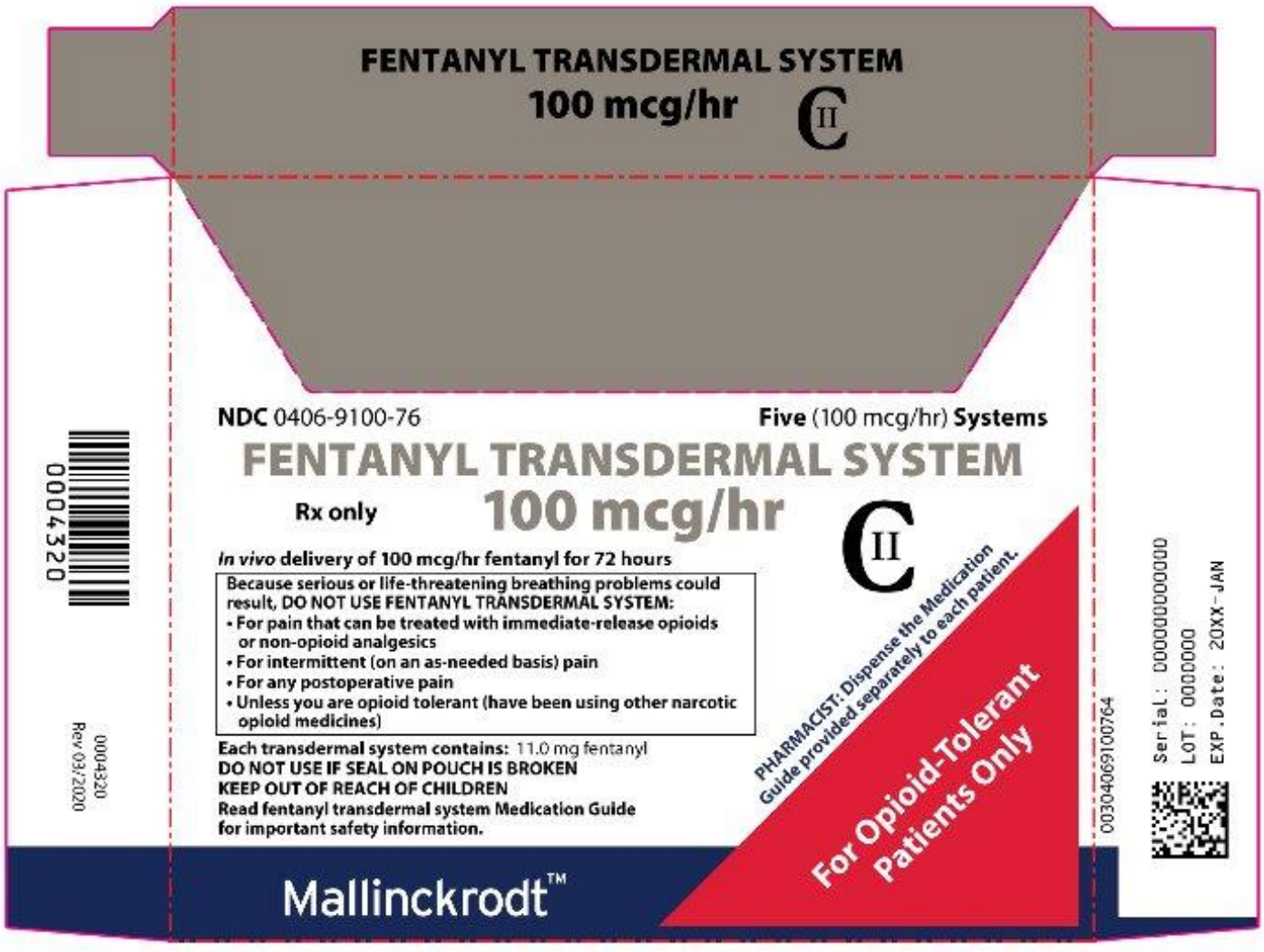

FENTANYL TRANSDERMAL

fentanyl transdermal patch, extended release

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:0406-9112
Route of Administration	TRANSDERMAL	**DEA Schedule**	CII

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
FENTANYL (UNII: UF599785JZ) (FENTANYL - UNII:UF599785JZ)	FENTANYL	12.5 ug in 1 h

Inactive Ingredients

Ingredient Name	Strength
HYDROXYPROPYL CELLULOSE (1200000 WAMW) (UNII: U3JF91U133)	
ETHYLENE-VINYL ACETATE COPOLYMER (19% VINYLACETATE) (UNII: JK6142KK4O)	
DIPROPYLENE GLYCOL (UNII: E107L85C40)	
DIMETHICONE (UNII: 92RU3N3Y1O)	
DIMETHICONE 350 (UNII: 2Y53S6ATLU)	
HEPTANE (UNII: 456148SDMJ)	

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0406-9112-76	5 in 1 CARTON	05/06/2020	
1		1 in 1 POUCH		
1		72 h in 1 PATCH; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA077154	05/06/2020	

FENTANYL TRANSDERMAL

fentanyl transdermal patch, extended release

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:0406-9125
Route of Administration	TRANSDERMAL	**DEA Schedule**	CII

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
FENTANYL (UNII: UF599785JZ) (FENTANYL - UNII:UF599785JZ)	FENTANYL	25 ug in 1 h

Inactive Ingredients	
Ingredient Name	**Strength**
HYDROXYPROPYL CELLULOSE (1200000 WAMW) (UNII: U3JF91U133)	
ETHYLENE-VINYL ACETATE COPOLYMER (19% VINYLACETATE) (UNII: JK6142KK4O)	
DIPROPYLENE GLYCOL (UNII: E107L85C40)	
DIMETHICONE (UNII: 92RU3N3Y1O)	
DIMETHICONE 350 (UNII: 2Y53S6ATLU)	
HEPTANE (UNII: 456148SDMJ)	

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1	NDC:0406-9125-76	5 in 1 CARTON	05/06/2020	
1		1 in 1 POUCH		
1		72 h in 1 PATCH; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA077154	05/06/2020	

FENTANYL TRANSDERMAL

fentanyl transdermal patch, extended release

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:0406-9037
Route of Administration	TRANSDERMAL	**DEA Schedule**	CII

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
FENTANYL (UNII: UF599785JZ) (FENTANYL - UNII:UF599785JZ)	FENTANYL	37.5 ug in 1 h

Inactive Ingredients	
Ingredient Name	**Strength**
HYDROXYPROPYL CELLULOSE (1200000 WAMW) (UNII: U3JF91U133)	
ETHYLENE-VINYL ACETATE COPOLYMER (19% VINYLACETATE) (UNII: JK6142KK4O)	
DIPROPYLENE GLYCOL (UNII: E107L85C40)	
DIMETHICONE (UNII: 92RU3N3Y1O)	
DIMETHICONE 350 (UNII: 2Y53S6ATLU)	

HEPTANE (UNII: 456148SDMJ)	

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1	NDC:0406-9037-76	5 in 1 CARTON	02/28/2020	
1		1 in 1 POUCH		
1		72 h in 1 PATCH; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA077154	02/28/2020	

FENTANYL TRANSDERMAL

fentanyl transdermal patch, extended release

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:0406-9150
Route of Administration	TRANSDERMAL	**DEA Schedule**	CII

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
FENTANYL (UNII: UF599785JZ) (FENTANYL - UNII:UF599785JZ)	FENTANYL	50 ug in 1 h

Inactive Ingredients	
Ingredient Name	**Strength**
HYDROXYPROPYL CELLULOSE (1200000 WAMW) (UNII: U3JF91U133)	
ETHYLENE-VINYL ACETATE COPOLYMER (19% VINYLACETATE) (UNII: JK6142KK4O)	
DIPROPYLENE GLYCOL (UNII: E107L85C40)	
DIMETHICONE (UNII: 92RU3N3Y1O)	
DIMETHICONE 350 (UNII: 2Y53S6ATLU)	
HEPTANE (UNII: 456148SDMJ)	

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1	NDC:0406-9150-76	5 in 1 CARTON	05/06/2020	
1		1 in 1 POUCH		

1		72 h in 1 PATCH; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA077154	05/06/2020	

FENTANYL TRANSDERMAL

fentanyl transdermal patch, extended release

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:0406-9062
Route of Administration	TRANSDERMAL	**DEA Schedule**	CII

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
FENTANYL (UNII: UF599785JZ) (FENTANYL - UNII:UF599785JZ)	FENTANYL	62.5 ug in 1 h

Inactive Ingredients

Ingredient Name	Strength
HYDROXYPROPYL CELLULOSE (1200000 WAMW) (UNII: U3JF91U133)	
ETHYLENE-VINYL ACETATE COPOLYMER (19% VINYLACETATE) (UNII: JK6142KK4O)	
DIPROPYLENE GLYCOL (UNII: E107L85C40)	
DIMETHICONE (UNII: 92RU3N3Y1O)	
DIMETHICONE 350 (UNII: 2Y53S6ATLU)	
HEPTANE (UNII: 456148SDMJ)	

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0406-9062-76	5 in 1 CARTON	02/28/2020	
1		1 in 1 POUCH		
1		72 h in 1 PATCH; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA077154	02/28/2020	

FENTANYL TRANSDERMAL

fentanyl transdermal patch, extended release

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:0406-9175
Route of Administration	TRANSDERMAL	**DEA Schedule**	CII

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
FENTANYL (UNII: UF599785JZ) (FENTANYL - UNII:UF599785JZ)	FENTANYL	75 ug in 1 h

Inactive Ingredients	
Ingredient Name	**Strength**
HYDROXYPROPYL CELLULOSE (1200000 WAMW) (UNII: U3JF91U133)	
ETHYLENE-VINYL ACETATE COPOLYMER (19% VINYLACETATE) (UNII: JK6142KK4O)	
DIPROPYLENE GLYCOL (UNII: E107L85C40)	
DIMETHICONE (UNII: 92RU3N3Y1O)	
DIMETHICONE 350 (UNII: 2Y53S6ATLU)	
HEPTANE (UNII: 456148SDMJ)	

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1	NDC:0406-9175-76	5 in 1 CARTON	05/06/2020	
1		1 in 1 POUCH		
1		72 h in 1 PATCH; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA077154	05/06/2020	

FENTANYL TRANSDERMAL

fentanyl transdermal patch, extended release

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:0406-9100

Route of Administration	TRANSDERMAL	DEA Schedule	CII

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
FENTANYL (UNII: UF599785JZ) (FENTANYL - UNII:UF599785JZ)	FENTANYL	100 ug in 1 h

Inactive Ingredients

Ingredient Name	Strength
HYDROXYPROPYL CELLULOSE (1200000 WAMW) (UNII: U3JF91U133)	
ETHYLENE-VINYL ACETATE COPOLYMER (19% VINYLACETATE) (UNII: JK6142KK4O)	
DIPROPYLENE GLYCOL (UNII: E107L85C40)	
DIMETHICONE (UNII: 92RU3N3Y1O)	
DIMETHICONE 350 (UNII: 2Y53S6ATLU)	
HEPTANE (UNII: 456148SDMJ)	

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0406-9100-76	5 in 1 CARTON	05/06/2020	
1		1 in 1 POUCH		
1		72 h in 1 PATCH; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA077154	05/06/2020	

Labeler - SpecGx LLC (080679498)

Establishment

Name	Address	ID/FEI	Business Operations
LTS Lohmann Therapy Systems Corp.		787660513	analysis(0406-9112, 0406-9125, 0406-9037, 0406-9150, 0406-9062, 0406-9175, 0406-9100) , manufacture(0406-9112, 0406-9125, 0406-9037, 0406-9150, 0406-9062, 0406-9175, 0406-9100)

Establishment

Name	Address	ID/FEI	Business Operations
SpecGx LLC		163205300	api manufacture(0406-9112, 0406-9125, 0406-9037, 0406-9150, 0406-9062, 0406-9175, 0406-9100)