WARNING: ADDICTION, ABUSE, AND MISUSE; LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL EXPOSURE; NEONATAL OPIOID WITHDRAWAL SYNDROME; CYTOCHROME P450 3A4 INTERACTION; AND EXPOSURE TO HEAT

Addiction, Abuse, and Misuse
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 fentanyl transdermal system, and monitor all patients regularly for the development of these behaviors or 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, even when used as recommended. Monitor for respiratory depression, especially during initiation of fentanyl transdermal system or following a dose increase. Because of the risk of respiratory depression, fentanyl transdermal system is contraindicated for use as an as-needed analgesic, in non-opioid-tolerant patients, in acute pain, and in postoperative pain (see Contraindications (4) and Warnings and Precautions (5.2)).

Accidental Exposure
Deaths due to a fatal 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)).

Neonatal Opioid Withdrawal Syndrome
Prolonged use of fentanyl transdermal system during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available (see Warnings and Precautions (5.4)).

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 CYP3A4 inhibitor or inducer (see Warnings and Precautions (5.10) and Clinical Pharmacology (12.3)).

Exposure To 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 and death (see Warnings and Precautions (5.11)). Patients wearing fentanyl transdermal systems who develop fever or increased core body temperature due to strenuous exertion are also at risk for increased fentanyl exposure and may require an adjustment in the dose of fentanyl transdermal system to avoid overdose and death (see Warnings and Precautions (5.12)).

1 INDICATIONS AND USAGE
Fentanyl transdermal system is indicated for the management of pain in opioid-tolerant patients, severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.

Patients considered opioid-tolerant are those who are taking, for one week or longer, at least 60 mg of morphine daily, or at least 30 mg of oral oxycodone daily, or at least 8 mg of oral hydrocodone daily, or an equianalgesic dose of another opioid.

Limitations of Use
• Because of the risks of addiction, abuse, and misuse with opioids, even when used as recommended, and because of the greater risks of overdose and death with extended-release opioid formulations, reserve fentanyl transdermal system for use in patients for whom alternative treatment options (i.e., non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain.

2 DOSAGE AND ADMINISTRATION
2.1 Initial Dosing
Fentanyl transdermal system should be prescribed only by healthcare professionals who are knowledgeable in the use of potent opioids for the management of chronic pain.

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 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.

Patients considered opioid-tolerant are those who are taking at least 60 mg of morphine daily, or at least 30 mg of oral oxycodone daily, or at least 8 mg of oral hydrocodone daily or an equianalgesic dose of another opioid for a week or longer.

Initiate the dosing regimen for each patient individually, taking into account the patient’s prior analgesic treatment experience and risk factors for addiction, abuse, and misuse (see Warnings and Precautions (5.1)). Monitor patients closely for respiratory depression, especially within the first 24 to 72 hours of initiating therapy with fentanyl transdermal system when serum concentrations from the initial patch will peak (see Warnings and Precautions (5.2)).

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. Discontinue all other around-the-clock opioid drugs when fentanyl transdermal system therapy is initiated.

While there are useful tables of opioid equivalents readily available, there is substantial interpatient variability in the relative potency of different opioid drugs and products. As such, it is preferable to underestimate a patient’s 24-hour fentanyl requirements and provide rescue medication (i.e., immediate-release opioid) than to overestimate the 24-hour fentanyl requirements which could result in adverse reactions. 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.

Consider the following when using the information in Table 1:
• This is not a table of equianalgesic doses.
• The conversion doses in this table are only for the conversion from one of the listed oral or parenteral opioid analgesics to fentanyl transdermal system.
• The table cannot be used to convert from fentanyl transdermal system to another opioid. Doing so will result in an overestimation of the dose of the new opioid and may result in fatal overdose.

To convert patients from oral or parenteral opioids to fentanyl transdermal system, use Table 1. Do not use Table 1 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 1: DOSE CONVERSION TO FENTANYL TRANSDERMAL SYSTEM

<table>
<thead>
<tr>
<th>Current Analgesic</th>
<th>Daily Dosage (mg/day)</th>
<th>Oral morphine</th>
<th>60 to 134</th>
<th>25</th>
<th>135 to 224</th>
<th>50</th>
<th>225 to 314</th>
<th>75</th>
<th>315 to 404</th>
<th>100</th>
<th>405 to 494</th>
<th>125</th>
<th>495 to 584</th>
<th>150</th>
<th>585 to 674</th>
<th>175</th>
<th>675 to 764</th>
<th>200</th>
<th>765 to 854</th>
<th>225</th>
<th>855 to 944</th>
<th>250</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transdermal System Dose</td>
<td>Oral 24 Hour Morphine (mg/day)</td>
<td>60 to 134</td>
<td>25</td>
<td>135 to 224</td>
<td>50</td>
<td>225 to 314</td>
<td>75</td>
<td>315 to 404</td>
<td>100</td>
<td>405 to 494</td>
<td>125</td>
<td>495 to 584</td>
<td>150</td>
<td>585 to 674</td>
<td>175</td>
<td>675 to 764</td>
<td>200</td>
<td>765 to 854</td>
<td>225</td>
<td>855 to 944</td>
<td>250</td>
<td></td>
</tr>
</tbody>
</table>

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

1 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 2 for conversion to other analgesics can overestimate the dose of the new agent. Overdosage of the new analgesic agent is possible (see Dosage and Administration (2.3)). Alternatively, for adult and pediatric patients taking opioids or doses not listed in Table 1, use the conversion methodology outlined above with Table 2.

2 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 to 134 | 25 | 135 to 224 | 50 | 225 to 314 | 75 | 315 to 404 | 100 | 405 to 494 | 125 | 495 to 584 | 150 | 585 to 674 | 175 | 675 to 764 | 200 | 765 to 854 | 225 | 855 to 944 | 250 | 945 to 1034 | 275 | 1035 to 1124 | 300 |
For delivery rates in excess of 100 mcg/hour, multiple systems may be used. For patients that may be more sensitive to the effects of opioids, additional intermediate strengths may be considered during conversion from prior opioids or titrating the dose of the fentanyl transdermal system. For example, rather than converting or titrating to a 50 mcg/hr system, a 37.5 mcg/hr system is available. 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, and an 87.5 mcg/hr system is available as an intermediate strength between the 75 mcg/hr system and the 100 mcg/hr system. The additional intermediate strengths, 32.5 mcg/hr, 62.5 mcg/hr and 87.5 mcg/hr, were not used in the clinical studies.

**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 sedation and respiratory depression, including at each dosage increase [see Warnings and Precautions (5.15), Use in Specific Populations (8.7) and Clinical Pharmacology (12.3)].

**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 sedation and respiratory depression, including at each dosage increase [see Warnings and Precautions (5.15), Use in Specific Populations (8.7) and Clinical Pharmacology (12.3)].

### 2.2 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 and the relative incidence of adverse reactions, as well as monitoring for the development of addiction, abuse, or misuse. 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 chronic therapy, periodically reassess the continued need for opioid analgesics. 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 unacceptable opioid-related adverse reactions are observed, the subsequent doses may be reduced. 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.

### 2.3 Administration of Fentanyl Transdermal System

**Fentanyl transdermal system patches 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-irritated 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 (i.e., cut) in any way prior to application. Fentanyl transdermal system should not be used if the patch 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 patch 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 patch occur, the edges of the patch may be taped with first aid tape. If problems with adhesion persist, the patch may be overlaid with a transparent adhesive film dressing (i.e., BIOCLUSIVE® or Askina®Derm).**

- **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.**

### 2.4 Disposal Instructions

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

Patients should dispose of used patches immediately upon removal by folding the adhesive side of the patch to itself, then flushing down the toilet. Unused patches should be removed from their pouches, the protective liners removed, the patches folded so that the adhesive side of the patch adheres to itself, and immediately flushed down the toilet.

Patients should dispose of any patches remaining from a prescription as soon as they are no longer needed.

### 2.5 Discontinuation of Fentanyl Transdermal System

Significant amounts of fentanyl continue to be absorbed from the skin for 24 hours or more after the patch is removed [see Clinical Pharmacology (12.3)]. To convert patients to another opioid, remove fentanyl transdermal system and titrate the dose of the new agonist based upon the patient’s report of pain until adequate analgesia has been attained. Upon system removal, 17 hours or more are required for a 50% decrease in serum fentanyl concentrations. Withdrawal symptoms are possible in some patients after conversion or dose adjustment [see Warnings and Precautions (5.17)].

Do not use Tables 1 and 2 to convert from fentanyl transdermal system to other therapies to avoid overestimating the dose of the new agent resulting in overdose of the new analgesic and possibly death.

When discontinuing fentanyl transdermal system and not converting to another opioid, use a gradual downward titration, such as halving the dose every 6 days, in order to reduce the possibility of withdrawal symptoms [see Warnings and Precautions (5.17)]. It is not known at what dose level fentanyl transdermal system may be discontinued without producing the signs and symptoms of opioid withdrawal.

### 3 DOSAGE FORMS AND STRENGTHS

Fentanyl transdermal system is available as:

- **Fentanyl Transdermal System 12 mcg/hour** (system size 3.13 cm²).
- **Fentanyl Transdermal System 25 mcg/hour** (system size 6.25 cm²).
- **Fentanyl Transdermal System 37.5 mcg/hour** (system size 9.38 cm²).
- **Fentanyl Transdermal System 50 mcg/hour** (system size 12.5 cm²).
- **Fentanyl Transdermal System 62.5 mcg/hour** (system size 15.63 cm²).
- **Fentanyl Transdermal System 75 mcg/hour** (system size 18.75 cm²).
- **Fentanyl Transdermal System 87.5 mcg/hour** (system size 21.88 cm²).
- **Fentanyl Transdermal System 100 mcg/hour** (system size 25 cm²).

*This lowest dosage is designated as 12 mcg/hour; however, the actual dosage is 12.5 mcg/hour to distinguish it from a 125 mcg/hour dosage that could be prescribed by multiple patches.*

### 4 CONTRAINDICATIONS

Fentanyl transdermal system is contraindicated in the following patients and situations:

- in patients who are not opioid-tolerant.
- in the management of acute or intermittent pain, or in patients who require opioid analgesia for a short period of time.
- in the management of post-operative pain, including use after out-patient or day surgeries, (i.e., tonsillectomies).
- in the management of mild pain.
- in patients with significant respiratory compromise, especially if adequate monitoring and resuscitative equipment are not readily available.
- in patients who have acute or severe bronchial asthma.
- in patients who have or are suspected of having paralytic ileus.
- in patients with known hypersensitivity to fentanyl or any components of the transdermal system. Severe hypersensitivity reactions, including anaphylaxis have been observed with fentanyl 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 [see Drug Abuse and Dependence (9)]. As modified-release products such as fentanyl transdermal system deliver the opioid over an extended period of time, there is a greater risk for overdose and death due to the larger amount of fentanyl present.
Although the risk of addiction in any individual is unknown, it can occur in patients appropriately prescribed fentanyl transdermal system and in those who obtain the drug illicitly. Addiction can occur at recommended doses and if the drug is misused or abused.

Assess each patient's risk for opioid addiction, abuse, or misuse prior to prescribing fentanyl transdermal system, and monitor all patients receiving fentanyl transdermal system for the development of these behaviors or conditions. Risks are increased in patients with a personal or family history of substance abuse (including drug or alcohol addiction), abuse or misuse, or mental illness (i.e., major depression). The potential for these risks should not, however, prevent the prescribing of fentanyl transdermal system for the proper management of pain in any given patient. Patients at increased risk may be prescribed modified-release opioid formulations 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 intensive monitoring for signs of addiction, abuse, and misuse.

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)].

Opioid agonists such as fentanyl transdermal system are sought by drug abusers and people with addiction disorders and are subject to criminal diversion. 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 the proper disposal of unused drug [see Patient Counseling Information (17)]. 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 from opioid use, if not immediately recognized and treated, may lead to respiratory arrest and death. Management of respiratory depression may include administration of oxygen, supportive measures, and use of opioid antagonists, depending on the patient's clinical status [see Overdosage (10)]. Carbon dioxide (CO₂) 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 dose increase. Closely monitor patients for respiratory depression when initiating therapy with fentanyl transdermal system.

- Reduce the risk of respiratory depression, proper dosing and titration of fentanyl transdermal system are essential [see Dosage and Administration (2.2)]. Overestimating the fentanyl transdermal system dose 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.

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 that can result in death. 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 (2.2), (2.5)].

5.4 Neonatal Opioid Withdrawal Syndrome

Prolonged use of fentanyl transdermal system during pregnancy can result in withdrawal signs 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. If opioid use is required for a prolonged period in a pregnant woman, considering the use of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available.

Neonatal opioid withdrawal syndrome presents as irritability, hyperactivity and abnormal sleep patterns, 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.

5.5 Interactions with Central Nervous System Depressants

Hypotension, profound sedation, coma, respiratory depression, and death may result if fentanyl transdermal system is used concomitantly with alcohol or other central nervous system (CNS) depressants (i.e., sedatives, anxiolytics, hypnotics, neuroleptics, other opioids). When considering the use of fentanyl transdermal system in a patient taking a CNS depressant, assess the duration use of the CNS depressant and the patient's response, including the degree of tolerance that has developed to CNS depression. Additionally, evaluate the patient's use of alcohol or illicit drugs that cause CNS depression. If the decision to begin fentanyl transdermal system is made, reduce the starting dose, monitor patients for signs of sedation and respiratory depression, and consider using a lower dose of the concomitant CNS depressant [see Drug Interactions (7.1)].

5.6 Use in Elderly, Cachetic, and Debilitated Patients

Life-threatening respiratory depression is more likely to occur in elderly, cachectic, or debilitated patients as they may have altered pharmacokinetics or altered clearance compared to younger, healthier patients. Monitor such 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)].

5.7 Chronic Pulmonary Disease

Monitor patients with significant chronic obstructive pulmonary disease or cor pulmonale, and patients having a substantially decreased respiratory reserve, hypoxia, hypercapnia, or preexisting respiratory depression for respiratory depression, particularly when initiating therapy with fentanyl transdermal system, as in these patients, even usual therapeutic doses of fentanyl transdermal system may decrease respiratory drive to the point of apnea [see Warnings and Precautions (5.2)]. Consider the use of alternative non-opioid analgesics in these patients if possible.

5.8 Head Injuries and Increased Intracranial Pressure

Avoid use of fentanyl transdermal system in patients who may be particularly susceptible to the intracranial effects of CO₂ retention such as those with evidence of increased intracranial pressure, head injuries, or coma. Intravenous opioids may exacerbate the sedating effects of opioids.

5.9 Hypotensive Effects

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 (i.e., phenothiazines or general anesthetics) [see Drug Interactions (7.1)]. Monitor these patients for signs of hypotension after initiating or titrating the dose of fentanyl transdermal system.

5.10 Interactions with CYP3A4 Inhibitors and Inducers

Since the CYP3A4 isozyme plays a major role in the metabolism of fentanyl transdermal system, using fentanyl transdermal system activity may cause changes in clearance of fentanyl which could lead to changes in fentanyl plasma concentrations. The concomitant use of fentanyl transdermal system with a CYP3A4 inhibitor (such as ritonavir, ketoconazole, itraconazole, telradomycin, clarithromycin, nefazodone, amiodarone, aprepitant, diltiazem, erythromycin, fluconazole, fosamprenavir, verapamil) 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 taking fentanyl transdermal system and any CYP3A4 inhibitor for signs of sedation and respiratory depression for an extended period of time, and make dosage adjustments as needed. CYP450 inducers, such as rifampin, carbamazepine, and phenytoin, may induce the metabolism of fentanyl and, therefore, may cause increased clearance of the drug which could lead to a decrease in fentanyl plasma concentrations, lack of efficacy or, possibly, development of an abstinence syndrome in a patient who had developed physical dependence to fentanyl. If co-administration is necessary, caution is advised when initiating fentanyl transdermal system treatment in patients currently taking, or discontinuing, CYP3A4 inhibitors or inducers. Evaluate these patients at frequent intervals and consider dose adjustments until stable drug effects are achieved [see Drug Interactions (7.2), and Clinical Pharmacology (12.3)].

5.11 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 (2.3)].

5.12 Patients with Fever

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 system who develop fever closely for opioid side effects 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.

5.13 Cardiac Disease

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

5.14 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. Closely monitor for signs of sedation and respiratory depression, including at each dosage increase [see Dosing and Administration (2.2), Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)].

5.15 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. Closely monitor for signs of sedation and respiratory depression, including at each dosage increase (see Dosing and Administration (2.2), Use in Specific Populations (8.7) and Clinical Pharmacology (12.3)).

5.16 Use in Pancreatic/Biliary Tract Disease
Fentanyl transdermal system may cause spasm of the sphincter of Oddi. Monitor patients with biliary tract disease, including acute pancreatitis for worsened symptoms. Fentanyl transdermal system may cause increases in the serum amylase concentration.

5.17 Avoidance of Withdrawal
Avoid the use of mixed agonist/antagonist (i.e., pentazocine, nalbuphine, and butorphanol) or partial agonist (buprenorphine) analgesics in patients who have received or are receiving a course of therapy with an 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.

5.18 Driving and Operating Machinery
Strong opioid analgesics impair the mental or physical abilities required for the performance of potentially dangerous tasks, such as driving a car or operating machinery. Warn patients not to drive or operate hazardous machinery unless they are tolerant to the effects of the fentanyl transdermal system.

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 (5.4))
- Interactions with Central Nervous System Depressants (see Warnings and Precautions (5.5))
- Hypotensive Effects (see Warnings and Precautions (5.8))

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.

6.1 Clinical Trial Experience
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 osteoarthritits 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 of patients with severe pain were nausea, vomiting, somnolence, dizziness, insomnia, constipation, hypotension, rash, pruritus, increasing at each dosage increase in ≥ 1% of patients) were headache, dizziness, insomnia, constipation, hypertension, rash, increasing at each dosage increase in ≥ 1% of patients) were headache, dizziness, insomnia, constipation, hypertension, rash, were reported in clinical trials of fentanyl transdermal system used for the treatment of chronic malignant or nonmalignant pain are shown in Table 3.

The most common adverse reactions that were associated with discontinuation in patients with pain (cause of discontinuation in ≥ 1% of patients) were headache, dizziness, somnolence, insomnia, constipation, hypertension, rash, and pruritus. 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 with an incidence greater than placebo-treated patients are shown in Table 3.

The most common adverse reactions 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: hypotension
- 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 for ≥ 1% fentanyl transdermal system-treated pediatric patients are shown in Table 5.

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

<table>
<thead>
<tr>
<th>System/Organ Class</th>
<th>Fentanyl Transdermal System</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>41% (N = 216)</td>
<td>17% (N = 200)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>26%</td>
<td>3%</td>
</tr>
<tr>
<td>Constipation</td>
<td>9%</td>
<td>1%</td>
</tr>
<tr>
<td>Abdominal pain upper</td>
<td>3%</td>
<td>2%</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>2%</td>
<td>0%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>6%</td>
<td>3%</td>
</tr>
<tr>
<td>Feeling cold</td>
<td>6%</td>
<td>2%</td>
</tr>
<tr>
<td>Malaise</td>
<td>4%</td>
<td>1%</td>
</tr>
<tr>
<td>Asthenia</td>
<td>2%</td>
<td>0%</td>
</tr>
<tr>
<td>Edema peripheral</td>
<td>1%</td>
<td>1%</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>5%</td>
<td>0%</td>
</tr>
<tr>
<td>Anorexia</td>
<td>5%</td>
<td>0%</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>4%</td>
<td>2%</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>System/Organ Class</th>
<th>Fentanyl Transdermal System</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>19% (N = 216)</td>
<td>3%</td>
</tr>
<tr>
<td>Dizziness</td>
<td>10%</td>
<td>4%</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>10%</td>
<td>7%</td>
</tr>
<tr>
<td>Depression</td>
<td>1%</td>
<td>0%</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>6%</td>
<td>1%</td>
</tr>
<tr>
<td>Pruritus</td>
<td>3%</td>
<td>2%</td>
</tr>
<tr>
<td>Rash</td>
<td>2%</td>
<td>1%</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>System/Organ Class</th>
<th>Fentanyl Transdermal System</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>24% (N = 289)</td>
</tr>
<tr>
<td>Constipation</td>
<td>13%</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>9%</td>
</tr>
<tr>
<td>Abdominal pain upper</td>
<td>4%</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>2%</td>
</tr>
<tr>
<td>Edema peripheral</td>
<td>5%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>2%</td>
</tr>
<tr>
<td>Application site reaction</td>
<td>1%</td>
</tr>
</tbody>
</table>
Table 5. Adverse Reactions Reported by ≥ 1% of Fentanyl Transdermal System-treated Pediatric Patients in 3 Clinical Trials of Fentanyl Transdermal System

<table>
<thead>
<tr>
<th>System/Organ Class</th>
<th>Fentanyl Transdermal System</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse Reaction</td>
<td>%</td>
</tr>
<tr>
<td>Common</td>
<td>1%</td>
</tr>
<tr>
<td>Asthenia</td>
<td>1</td>
</tr>
<tr>
<td>Immune system disorders</td>
<td>3</td>
</tr>
<tr>
<td>Hypersensitivity</td>
<td>2</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>2</td>
</tr>
<tr>
<td>Muscle spasms</td>
<td>2</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>2</td>
</tr>
<tr>
<td>Headache</td>
<td>1</td>
</tr>
<tr>
<td>Somnolence</td>
<td>1</td>
</tr>
<tr>
<td>Dizziness</td>
<td>1</td>
</tr>
<tr>
<td>Hypoesthesia</td>
<td>1</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>1</td>
</tr>
<tr>
<td>Insomnia</td>
<td>1</td>
</tr>
<tr>
<td>Anxiety</td>
<td>1</td>
</tr>
<tr>
<td>Depression</td>
<td>1</td>
</tr>
<tr>
<td>Hallucination</td>
<td>1</td>
</tr>
<tr>
<td>Urinary retention</td>
<td>1</td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td>1</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>1</td>
</tr>
<tr>
<td>Respiratory depression</td>
<td>1</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>1</td>
</tr>
<tr>
<td>Rash</td>
<td>1</td>
</tr>
<tr>
<td>Pruritus</td>
<td>1</td>
</tr>
<tr>
<td>Hypehidrosis</td>
<td>1</td>
</tr>
<tr>
<td>Erythema</td>
<td>1</td>
</tr>
</tbody>
</table>

6.2 Post-Marketing 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.

Cardiac Disorders: tachycardia, bradycardia
Eye Disorders: vision blurred
Gastrointestinal Disorders: ileus, dyspepsia
General Disorders and Administration Site Conditions: pyrexia
Immunosuppression System Disorders: anaphylactic shock, anaphylactic reaction, anaphylactoid reaction
Investigations: weight decreased
Nervous System Disorders: convulsions (including 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, hyperventilation, dyspnea
Vascular Disorders: hypotension, hypertension

7 DRUG INTERACTIONS

7.1 Central Nervous System Depressants

The concomitant use of fentanyl transdermal system with other CNS depressants, including sedatives, hypnotics, tranquilizers, general anesthetics, phenothiazines, other opioids, and alcohol, can increase the risk of respiratory depression, profound sedation, coma and death. Monitor patients receiving CNS depressants and fentanyl transdermal system for signs of respiratory depression, sedation and hypotension.

When combined therapy with any of the above medications is considered, the dose of one or both agents should be reduced [see Dosage and Administration (2.2) and Warnings and Precautions (5.5)].

7.2 Drugs Affecting Cytochrome P450 3A4 Isoenzymes

Inhibitors of CYP3A4: Because the CYP3A4 isoenzyme plays a major role in the metabolism of fentanyl, drugs that inhibit CYP3A4 activity may cause decreased clearance of fentanyl which could lead to an increase in fentanyl plasma concentrations and result in increased or prolonged opioid effects. These effects could be more pronounced with concomitant use of 3A4 inhibitors. If coadministration with fentanyl transdermal system is necessary, monitor patients for respiratory depression and sedation at frequent intervals and consider dose adjustments until stable drug effects are achieved [see Clinical Pharmacology (12.3)].

Inducers of CYP3A4: CYP450 3A4 inducers may induce the metabolism of fentanyl and, therefore, may cause increased clearance of the drug which could lead to a decrease in fentanyl plasma concentrations, lack of efficacy or, possibly, development of a withdrawal syndrome in a patient who had developed physical dependence to fentanyl. If co-administration with fentanyl transdermal system is necessary, monitor for signs of opioid withdrawal and consider dose adjustments until stable drug effects are achieved [see Clinical Pharmacology (12.3)].

After stopping the treatment of a CYP3A4 inducer, as the effects of the inducer decline, the fentanyl plasma concentration will increase which could increase or prolong both the therapeutic and adverse effects, and may cause serious respiratory depression [see Clinical Pharmacology (12.3)].

7.3 MAO Inhibitors

Avoid use of fentanyl transdermal system in the patient who would require the concomitant administration of a monoamine oxidase (MAO) inhibitor, or within 14 days of stopping such treatment because severe and unpredictable potentiation by MAO inhibitors has been reported with opioid analgesics.

7.4 Mixed Agonist/Antagonist and Partial Agonist Opioid Analgesics

Mixed agonist/antagonist (i.e., pentazocine, nalbuphine, and butorphanol) and partial agonist (buprenorphine) analgesics may reduce the analgesic effect of fentanyl transdermal system or may precipitate withdrawal symptoms. Avoid the use of agonist/antagonist and partial agonist analgesics in patients receiving fentanyl transdermal system.

7.5 Anticholinergics

Anticholinergics or other medications with anticholinergic activity when used concurrently with opioid analgesics may result in increased risk of urinary retention and/or severe constipation, which may lead to paralytic ileus. Monitor patients for signs of urinary retention or reduced gastrointestinal motility when fentanyl transdermal system is used concurrently with anticholinergic drugs.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Clinical Considerations

Fetal/neonatal adverse reactions: Prolonged use of opioid analgesics during pregnancy for medical or nonmedical purposes can result in physical dependence in the neonate and neonatal opioid withdrawal syndrome shortly after birth. Observe newborns for symptoms of neonatal opioid withdrawal syndrome, such as poor feeding, diarrhea, irritability, tremor, rigidity, and seizures, and manage accordingly [see Warnings and Precautions (5.4)].

Teratogenic Effects

Pregnancy C: 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.

The potential effects of fentanyl on embryo-fetal development were studied in the rat, mouse, and rabbit models. Published literature reports that administration of fentanyl (0, 10, 100, or 500 mcg/kg/day) to pregnant female Sprague-Dawley rats from day 7 to 21 via implanted micro osmotic minipumps did not produce any evidence of teratogenicity (the high dose is approximately 2 times the daily human dose administered by a 100 mcg/hr patch on a mg/m2 basis). In contrast, the intravenous administration of fentanyl (0.01, 0.03 mg/kg) to bred female 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. 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 intrauterine 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 attributable 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/m2 basis).

Nonteratogenic Effects

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 intrauterine or epidural fentanyl. Transient neonatal muscular rigidity has been observed in infants whose mothers were treated with intravenous fentanyl.

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 intrauterine 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/m2 basis.

8.2 Labor and Delivery

Opioids cross the placenta and may produce respiratory depression in neonates. Fentanyl transdermal system is not for use in women during and immediately prior to labor, when shorter acting analgesics or other analgesic techniques are more appropriate. Opioid analgesics 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.

8.3 Nursing Mothers

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

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/h 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 (2.4), (2.5) 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, dose selection for an elderly patient should be cautious, 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 patch 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)].

Monitor geriatric patients closely for signs of sedation and respiratory depression, particularly when initiating therapy with fentanyl transdermal system and when given in conjunction with other drugs that depress respiration [see Warnings and Precautions (5.2), (5.6)].

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 hepatic contribution to the elimination of fentanyl transdermal system, hepatic impairment may 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 Dosing and Administration (2.1), Warnings and Precautions (5.14) 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 Dosing and Administration (2.1), Warnings and Precautions (5.15) and Clinical Pharmacology (12.3)].

9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
Fentanyl transdermal system contains fentanyl, a Schedule II controlled substance with a high potential for abuse similar to other opioids including morphine, hydromorphone, methadone, oxycodone, and oxymorphone. Fentanyl transdermal system can be abused and is subject to misuse, addiction, and criminal diversion [see Warnings and Precautions (5.1)].

The high drug content in extended-release formulations adds to the risk of adverse outcomes from abuse and misuse.

9.2 Abuse
All patients treated with opioids require careful monitoring for signs of abuse and addiction, since use of opioid agonist drugs carries the risk of addiction even under appropriate medical use. Drug abuse is the intentional non-therapeutic use of an over-the-counter or prescription drug, even once, for its rewarding psychological or physiological effects. Drug abuse includes, but is not limited to, the following examples: the use of a prescription or over-the-counter drug to get “high”, or the use of steroids for performance enhancement and muscle build up.

Drug abuse is a cluster of behavioral, cognitive, and physiological phenomena that develop after repeated substance use and include: a strong desire to take the drug, difficulties in controlling its use, persisting in its use despite harmful consequences, a higher priority given to drug use than to other activities and obligations, increased tolerance, and sometimes a physical withdrawal. “Drug seeking” behavior is very common in addicts and drug abusers. 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 physician(s). "Doctor shopping" to obtain additional prescriptions is common among drug abusers and people suffering from untreated addiction. Preoccupation with achieving pain relief can be appropriate behavior in a patient with poor pain control. Abuse and addiction are separate and distinct from physical dependence and tolerance. Physicians should be aware that addiction may be accompanied by concurrent tolerance and symptoms of physical dependence in all addicts. Fentanyl transdermal system, like other opioids, can be diverted for non-medical use into illicit channels of distribution. Careful recordkeeping of prescribing information, including quantity, frequency, and renewal requests, as required by state 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. The risk of overdose increased with concurrent abuse of fentanyl transdermal system with alcohol and other central nervous system depressants [see Warnings and Precautions (5.5), and Drug Interactions (7.1)]. 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 chronic opioid therapy. Tolerance is the need for increasing doses of opioids to maintain a defined effect such as analgesia (in the absence of disease progression or other external factors). Tolerance may occur to both the desired and undesirable effects of drugs, and may develop at different rates for different effects.

Physical dependence results in withdrawal symptoms after abrupt discontinuation or a significant dose reduction of a drug. Withdrawal also may be precipitated through the administration of drugs with opioid antagonist activity, i.e., naxalone, nalmeine, mixed agonist/antagonist analgesics (pentazocine, butorphanol, nalbuphine), or partial agonists (buprenorphine). Physical dependence may not occur to a clinically significant degree until after several days to weeks of continued opioid usage.

Fentanyl transdermal system should not be abruptly discontinued [see Dosage and Administration (2.5)]. If fentanyl transdermal system is abruptly discontinued in a physically-dependent patient, an abstinence syndrome may occur. Some or all of the following can characterize this syndrome: 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.

Infants born to mothers physically dependent on opioids will also be physically dependent and may exhibit respiratory difficulties and withdrawal symptoms [see Use in Specific Populations (8.2, 8.3)].

10 OVERDOSAGE
10.1 Clinical Presentation
Acute overdosage with opioids can be manifested by respiratory depression, somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, constricted pupils, and sometimes bradycardia, hypotension and death. The pharmacokinetic characteristics of fentanyl transdermal system must also be taken into account when treating the overdose. Even in the face of improvement, continued medical monitoring is required because of the possibility of extended effects. Deaths due to overdose have been reported with abuse and misuse of fentanyl transdermal system.

10.2 Treatment of Overdose
Give primary attention to the reestablishment of a patent airway and institution of assisted or controlled ventilation. Employ supportive measures (including oxygen and vasopressors) in the management of circulatory shock and pulmonary edema accompanying overdose as indicated. Cardiac arrest or arrhythmias will require advanced life support techniques. Remove all fentanyl transdermal system systems.

The pure opioid antagonists, such as naloxone, are specific antidotes to respiratory depression from opioid overdose. Since the duration of reversal is expected to be less than the duration of action of fentanyl, 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.

Only administer opioid antagonists in the presence of clinically significant respiratory or circulatory depression secondary to hydromorphone overdose. In patients who are physically dependent on any opioid agonist including fentanyl transdermal system, an abrupt or complete reversal of opioid effects may precipitate an acute abstinence syndrome. The severity of the withdrawal syndrome produced will depend on the degree of physical dependence and the dose of the antagonist administered. Please see the prescribing information for the specific opioid antagonist for details of their proper use.

11 DESCRIPTION
Fentanyl transdermal system is a transdermal system containing fentanyl. The chemical name is N-Phenyl-N-(1-(2-phenylethyl)-4-piperidinyl) propanamide. The structural formula is:

The molecular weight of fentanyl base is 336.5, and the molecular formula is C29H27NO. The n-octanol: water partition coefficient is 8601. The pkA is 8.4.

System Components and Structure: The amount of fentanyl released from each system per hour is proportional to the surface area (25 mcg/hr per 6.25 cm2). The composition per unit area of all system sizes is identical.

<table>
<thead>
<tr>
<th>Dose</th>
<th>Size</th>
<th>Fentanyl Content</th>
</tr>
</thead>
<tbody>
<tr>
<td>mcg/hr</td>
<td>cm²</td>
<td>mg</td>
</tr>
<tr>
<td>12.5</td>
<td>3.13</td>
<td>1.28</td>
</tr>
<tr>
<td>25</td>
<td>6.25</td>
<td>2.55</td>
</tr>
<tr>
<td>37.5</td>
<td>9.38</td>
<td>3.83</td>
</tr>
<tr>
<td>50</td>
<td>12.5</td>
<td>5.10</td>
</tr>
<tr>
<td>62.5</td>
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<td>7.65</td>
</tr>
<tr>
<td>87.5</td>
<td>21.88</td>
<td>8.93</td>
</tr>
<tr>
<td>100</td>
<td>25</td>
<td>10.20</td>
</tr>
</tbody>
</table>

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

Fentanyl transdermal system is a transparent rectangular patch with rounded corners comprising a protective liner and two functional layers. Proceeding from the outer surface toward the surface...
adhering to skin, these layers are: 1) a backing layer of polyolefin film; 2) a drug-in-adhesive layer containing fentanyl as the active ingredient and silicone adhesive and dimethicone NF as inactive ingredients. Before use, a protective liner covering the adhesive layer is removed and discarded.

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

12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
Fentanyl is an opioid analgesic. Fentanyl interacts predominately with the opioid mu-receptor. These mu-binding sites are distributed in the human brain, spinal cord, and other tissues.

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

Fentanyl induces its principal pharmacologic effects on the central nervous system. Central nervous system effects increase with increasing serum fentanyl concentrations especially for patients who have an underlying pulmonary condition or who receive concomitant agents 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, post-marketing reports have been received that describe opioid-naïve post-operative patients who have experienced clinically significant hypoventilation and death with fentanyl transdermal system.

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

Ventilatory Effects: In clinical trials of 357 non-opioid tolerant subjects treated with fentanyl transdermal system experiences hypoventilation. Hypoventilation was associated by respiratory rates of less than 8 breaths/minute or a pCO2 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, post-marketing reports have been received that describe opioid-naïve 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.

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

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

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

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.

12.2 Pharmacodynamics Central Nervous System Effects: Fentanyl exerts its principal pharmacologic effects on the central nervous system. Central nervous system effects increase with increasing serum fentanyl concentrations.

Systemic availability of fentanyl delivered transdermally has not been determined.

While there is variation in dose delivered among patients, the nominal flux of the systems is sufficiently accurate as to allow individual titration of dosage for a given patient. 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 mcg, 25 mcg, 50 mcg, 62.5 mcg, 75 mcg, 87.5 mcg, 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 6). 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.

The kinetics of fentanyl in normal subjects following application of a 25 mcg/hr fentanyl transdermal system were bioequivalent with or without either BIOCLUSIVE® or Askina® Derm overlay (polyurethane film dressing).

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

<table>
<thead>
<tr>
<th>Fentanyl Transdermal System</th>
<th>Mean (SD) Time to Maximum Concentration</th>
<th>Mean (SD) Concentration at Maximum</th>
</tr>
</thead>
<tbody>
<tr>
<td>12 mcg/hr</td>
<td>28.8 (13.7)</td>
<td>0.38 (0.13)*</td>
</tr>
<tr>
<td>25 mcg/hr</td>
<td>31.7 (16.5)</td>
<td>0.85 (0.26)**</td>
</tr>
<tr>
<td>50 mcg/hr</td>
<td>38.0 (16.5)</td>
<td>1.72 (0.53)**</td>
</tr>
<tr>
<td>75 mcg/hr</td>
<td>35.8 (14.1)</td>
<td>2.32 (0.86)**</td>
</tr>
<tr>
<td>100 mcg/hr</td>
<td>29.9 (13.3)</td>
<td>3.36 (1.28)**</td>
</tr>
</tbody>
</table>

* Cmax values dose normalized from 4 x 12.5 mcg/hr; Study 2003-038 in healthy volunteers
** Cmax 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.

Following Single and Multiple Applications of Fentanyl Transdermal System 100 mcg/hr

Table 7: RANGE OF PHARMACOKINETIC PARAMETERS OF INTRAVENTRICAL FENTANYL IN PATIENTS

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clearance</td>
<td>(L/hr)</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(70 kg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Volume of Distribution</td>
<td>(L/Kg)</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Half-Life</td>
<td>(hr)</td>
<td></td>
</tr>
<tr>
<td>Surgical Patients</td>
<td>27 to 75</td>
<td>3 to 8</td>
</tr>
<tr>
<td>Heparinically Impaired Patients</td>
<td>3 to 80+</td>
<td>0.8 to 8+</td>
</tr>
<tr>
<td>Renally Impaired Patients</td>
<td>30 to 78</td>
<td>4 to 12+</td>
</tr>
</tbody>
</table>

*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).

Metabolism: Fentanyl is metabolized primarily via human cytochrome P450 3A4 isozyme 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.

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%.

Skin does not appear to metabolize fentanyl delivered transdermally. This was determined in a human keratinocyte cell assay and in clinical studies in which 52% of the dose delivered from the system was accounted for as unchanged fentanyl that appeared in the systemic circulation.

Specific Populations Geriatric Use: 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 Cmax 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 (34.4 hours versus 23.5 hours) [see Warnings and Precautions (5.6) and Use in Specific Populations (8.5)].

Pediatric Use: 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,
16 HOW SUPPLIED/STORAGE AND HANDLING

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

<table>
<thead>
<tr>
<th>Fentanyl Transdermal System Dose (mcg/hr)</th>
<th>System Size (cm²)</th>
<th>Fentanyl Content (mg)</th>
<th>NDC Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fentanyl Transdermal System – 12*</td>
<td>3.13</td>
<td>1.28</td>
<td>0378-9119-98</td>
</tr>
<tr>
<td>Fentanyl Transdermal System – 25</td>
<td>6.25</td>
<td>2.55</td>
<td>0378-9121-98</td>
</tr>
<tr>
<td>Fentanyl Transdermal System – 37.5</td>
<td>9.33</td>
<td>3.83</td>
<td>0378-9125-98</td>
</tr>
<tr>
<td>Fentanyl Transdermal System – 50</td>
<td>12.5</td>
<td>5.10</td>
<td>0378-9122-98</td>
</tr>
<tr>
<td>Fentanyl Transdermal System – 62.5</td>
<td>15.63</td>
<td>6.38</td>
<td>0378-9126-98</td>
</tr>
<tr>
<td>Fentanyl Transdermal System – 75</td>
<td>18.75</td>
<td>7.65</td>
<td>0378-9123-98</td>
</tr>
<tr>
<td>Fentanyl Transdermal System – 87.5</td>
<td>21.88</td>
<td>8.93</td>
<td>0378-9127-98</td>
</tr>
<tr>
<td>Fentanyl Transdermal System – 100</td>
<td>25</td>
<td>10.20</td>
<td>0378-9124-98</td>
</tr>
</tbody>
</table>

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

Store in original unopened pouch. Store at 20° to 25°C (68° to 77°F). [See USP Controlled Room Temperature.]

17 PATIENT COUNSELING INFORMATION

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

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 or 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 and can be increased if the dose is increased, that it can occur even at recommended doses [see Warnings and Precautions (5.2)]. Advise patients how to recognize respiratory depression and to seek medical attention if breathing difficulties develop.

Accidental Exposure: Inform patients to keep fentanyl transdermal system in a secure place out of the reach of children due to the high risk of 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.

Neonatal Opioid Withdrawal Syndrome: Inform female patients of reproductive potential that prolonged use of fentanyl transdermal system during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated [see Warnings and Precautions (5.4)].

Interactions with Alcohol and other CNS Depressants: Inform patients that potentially serious additive effects may occur if fentanyl transdermal system is used with alcohol or other CNS depressants, and not to use such drugs unless supervised by a healthcare provider.

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.

When no longer needed, advise patients how to safely taper fentanyl transdermal system and not to stop it abruptly to avoid the risk of precipitating withdrawal symptoms.

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 water beds.

Driving or Operating Heavy Machinery: Fentanyl transdermal system may impair mental and/or physical ability required for the performance of potentially hazardous tasks (i.e., driving, operating machinery). Instruct patients to refrain from any potentially dangerous activity when starting on fentanyl transdermal system or when their dose is being adjusted, until it is established that they have not been adversely affected.

Preparatory: Advise women of childbearing potential who become, or are planning to become pregnant, to consult a healthcare provider prior to initiating or continuing therapy with fentanyl transdermal system.

Additive Effects of Alcohol and other CNS Depressants: Instruct patients not to use alcohol or other CNS depressants (i.e., sleep medications, tranquilizers) while using fentanyl transdermal system because dangerous additive effects may occur, resulting in serious injury or death.

Constipation: Advise patients of the potential for severe constipation.

Disposal: Instruct patients to refer to the Instructions for Use for proper disposal of fentanyl transdermal system. To properly dispose of a used patch, instruct patients to remove it, fold so that the adhesive side of the patch adheres to itself, and immediately flush down the toilet. Unused patches should be removed from their pouches, the protective liners removed, the patches folded so that the adhesive side of the patch adheres to itself, and immediately flushed down the toilet.

Instruct patients to dispose of any patches remaining from a prescription as soon as they are no longer needed.
Fentanyl Transdermal System is:

- A strong prescription pain medicine that contains an opioid (narcotic) that is used to manage pain severe enough to require daily around-the-clock, long-term treatment with an opioid, in people who are already regularly using opioid pain medicine, when other pain treatments such as non-opioid pain medicines or immediate-release opioid 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 for use to treat pain that is not around-the-clock.

Important information about Fentanyl Transdermal System:

- Get emergency help 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.
- Never give anyone else your fentanyl transdermal system. They could die from using it. Store fentanyl transdermal system away from children and in a safe place to prevent stealing or abuse. Selling or giving away fentanyl transdermal system is against the law.
- 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.
- Proper disposal of fentanyl transdermal system after use and for unused patches when no longer needed: Fold the sticky sides of the patch together and flush down the toilet. Do not put patches in a trash can.

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
- liver, kidney, thyroid problems
- problems urinating
- pancreas or gallbladder problems
- abuse of street or prescription drugs, alcohol addiction, or mental health problems.

Tell your healthcare provider if you:

- have a fever
- are pregnant or planning to become pregnant. Prolonged use of fentanyl transdermal system during pregnancy can cause withdrawal symptoms in your newborn baby that could be life-threatening if not recognized and treated.
- are breastfeeding. Fentanyl transdermal system passes into breast milk and may harm your baby.
- 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.
- See the detailed Instructions for Use for information about how to apply and dispose of the fentanyl transdermal system.
- 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 patch continuously for 3 days, unless advised otherwise by your healthcare provider.
- 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.

Get emergency medical help 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, or you are feeling faint.

These are not all the possible side effects of fentanyl transdermal system. Call your doctor 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

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Manufactured for: Mylan Pharmaceuticals Inc. Morgantown, WV 26505 U.S.A. www.mylan.com or call 1-877-446-3679

REVISED MAY 2014
MG:FTS:R8
Instructions for Use
Fentanyl Transdermal System CII
(fen’ ta nil)

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

Parts of the fentanyl transdermal system:

- Protective film
- Backing layer
- Drug containing layer
- Protective liner

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 8 different doses and patch sizes. Make sure you have the right dose patch or patches that have been prescribed for you.

Applying a fentanyl transdermal system

1. Skin areas where the fentanyl transdermal system may be applied:
   - 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 A-D).
   - For children (and adults with mental impairment):
     - Put the patch on the upper back (See Figure B). This will lower the chances that the child will remove the patch and put it in their mouth.
   - For adults and children:
     - Do not 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 E).

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: Tear at notch and remove the fentanyl transdermal system. Each fentanyl transdermal system is packaged with additional pieces of protective film above and below the patch and 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 F). The additional pieces of protective film are discarded at time of use (See Figure G).

4. Peel: Peel off both parts of the protective liner from the patch. Each fentanyl transdermal system has a clear plastic liner that can be peeled off in two pieces. This covers the sticky side of the patch. Carefully peel this liner off. Throw the clear plastic liner away. Touch the sticky side of the fentanyl transdermal system as little as possible (See Figure H).

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 I). Make sure it sticks well, especially at the edges.
   - Fentanyl transdermal system may not stick to all patients. You need to check the patches often to make sure that they are 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 sticking, you may cover the patch with BIOCLUSIVE® or Askina®Derm. These are special see-through adhesive dressings. Never cover a fentanyl transdermal system with any other bandage or tape. Remove the liner from the BIOCLUSIVE® or Askina®Derm dressing and place it carefully over the fentanyl transdermal system, smoothing it over the patch and your skin.

   - If your patch falls off later, but before 3 days (72 hours) of use, 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).

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). 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 J). Flush the used fentanyl transdermal system down the toilet right away (See Figure K). 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 trashcan.

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

BIOCLUSIVE® is a registered trademark of Systagenix Wound Management, Inc.
Askina®Derm is a registered trademark of BBraun Melsungen AG

For more information, call Mylan Pharmaceuticals Inc. at 1-877-446-3679 (1-877-4-INFO-RX).