DURAGESIC® (Fentanyl Transdermal System)®

Full Prescribing Information

FOR USE IN OPIOID-TOLERANT PATIENTS ONLY

DURAGESIC® contains a high concentration of a potent Schedule II opioid agonist, fentanyl. Schedule II opioid substances which include fentanyl, hydromorphone, methadone, morphine, oxycodone, and oxymorphone have the highest potential for abuse and associated risk of fatal overdose due to respiratory depression. Fentanyl can be abused and is subject to criminal diversion. The high content of fentanyl in the patches (DURAGESIC®) makes it a particular target for abuse and diversion.

DURAGESIC® is indicated for management of persistent, moderate to severe chronic pain that:
• requires continuous, around-the-clock opioid administration for an extended period of time, and
• cannot be managed by other means such as non-steroidal analgesics, opioid combination products, or immediate-release opioids.

DURAGESIC® should only be used in patients who are already receiving opioid therapy, who have demonstrated opioid tolerance, and who require a total daily dose at least equivalent to a 25 mcg/h of DURAGESIC® 25 mcg/h. Patients who were on or were considered opioid-tolerant are those who have been taking, for a 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 hydromorphone daily or an equianalgesic dose of another opioid.

Because serious or life-threatening hypotention could occur, DURAGESIC® (fentanyl transdermal system) is contraindicated:
• in patients who are not opioid-tolerant
• in the management of acute 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 (e.g., tonsillectomies)
• in the management of mild pain
• in the management of intermittent pain (e.g., use on an as needed basis [prn])

Since the peak fentanyl concentrations generally occur between 20 and 72 hours of treatment, prescribers should be aware that serious or life threatening hypotention may occur, even in opioid-tolerant patients, during the initial application period.

The concurrent use of DURAGESIC® with all cytochrome P450 3A4 inhibitors (such as ritonavir, ketoconazole, itraconazole, telithromycin, clarithromycin, nefazodone, amiodarone, amprenavir, aprepitant, diltiazem, erythromycin, fluconazole, fosamprenavir, grapefruit juice, and 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. Patients receiving DURAGESIC® and any CYPSA inhibitor should be carefully monitored for an extended period of time and dosage adjustments should be made if warranted (see CLINICAL PHARMACOLOGY – Drug Interactions, WARNINGS, PRECAUTIONS, and DOSAGE AND ADMINISTRATION for further information).

The safety of DURAGESIC® has not been established in children under 2 years of age. DURAGESIC® should be administered to children only if they are opioid-tolerant and 2 years of age or older (see PRECAUTIONS – Pediatric Use).

DURAGESIC® is ONLY FOR use in patients who are already tolerant to opioid therapy of comparable potency. Use in non-opioid-tolerant patients may lead to fatal respiratory depression. Overestimating the DURAGESIC® dose when converting patients from another opioid medication can result in fatal overdose with the first dose (see DOSAGE AND ADMINISTRATION – Initial DURAGESIC® Dose Selection). Due to the mean half-life of approximately 20-27 hours, patients who have thought to have had a serious adverse event, including overdose, will require monitoring and treatment for at least 24 hours.

DURAGESIC® can be abused in a manner similar to other opioid agonists, legal or illicit. This risk should be considered when administering, prescribing, or dispensing DURAGESIC® in situations where the healthcare professional is concerned about increased risk of misuse, abuse, or diversion.

Persons at increased risk for opioid abuse include those with a personal or family history of substance abuse (including drug or alcohol abuse or addiction) or mental illness (e.g., major depression). Patients should be assessed for their clinical risks for opioid abuse and addiction prior to being prescribed opioids. All patients receiving opioids should be routinely monitored for signs of misuse, abuse, and addiction. Patients at increased risk of opioid misuse should be appropriately treated with modified-release opioid formulations; however, these patients will require intensive monitoring for signs of misuse, abuse, or diversion.

DURAGESIC® patches are intended for transdermal use (on intact skin) only. Do not use a DURAGESIC® patch if the pouch seal is broken or the patch is cut, damaged, or changed in any way.

Avoid exposing the DURAGESIC® application site and surrounding area to direct external heat sources, such as heating pads or electric blankets, heating lamps, saunas, hot tubs, and heated water beds, while wearing the system. Avoid taking hot baths or sunbathing. There is a potential for temperature-dependent increases in fentanyl released from the system resulting in possible overdose and death. Patients wearing DURAGESIC® systems who develop fever or increased core body temperature due to strenuous exercise should be monitored for opioid side effects and the DURAGESIC® dose should be adjusted if necessary.

DESCRIPTION

DURAGESIC® (fentanyl transdermal system) is a transdermal system providing continuous systemic delivery of fentanyl, a potent opioid analgesic, for 72 hours. The chemical name is N-Phenyl-N-(1-g-benzyl-4-piperidino)propanamide. The structural formula is:

The molecular weight of fentanyl base is 336.5, and the empirical formula is C20H24N2O. The n-octanol/water partition coefficient is 860.1. The pKa is 8.4.

System Components and Structure

The amount of fentanyl released from each system per hour is proportional to the surface area (25 mcg/h per 10.5 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>125</td>
<td>2.1</td>
<td>21.5</td>
</tr>
<tr>
<td>25</td>
<td>4.2</td>
<td>21.5</td>
</tr>
<tr>
<td>50</td>
<td>8.4</td>
<td>21.5</td>
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<tr>
<td>75</td>
<td>12.6</td>
<td>21.5</td>
</tr>
<tr>
<td>100</td>
<td>16.8</td>
<td>21.5</td>
</tr>
</tbody>
</table>

Note: Nominal delivery rate per hour
“Nominal delivery rate is 12.5 mcg/hr

DURAGESIC® is a rectangular transparent unit comprising a protective liner and two functional layers. Patches lying on the outer surface toward the surface adhering to skin, these layers are:
• 1) a backing layer of polyester/ethyl vinyl acetate film; 2) a drug-in-adhesive layer. Before use, a protective liner covering the adhesive layer is removed and discarded.

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

CLINICAL PHARMACOLOGY

Pharmacology

Fentanyl is an opioid analgesic. Fentanyl interacts predominately with the opioid mu-receptor. These mu-binding sites are discretely distributed in the human brain, spinal cord, and other tissues. In clinical settings, fentanyl exerts its principal pharmacologic effects on the central nervous system. 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. Analogic blood concentrations of fentanyl may cause nausea and vomiting directly stimulating the chemoreceptor trigger zone, but nausea and vomiting are significantly more common in ambulatory than in recumbent patients, as is postural syncope.

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

While opioids generally increase the tone of urinary tract smooth muscle, the net effect tends to be variable, since some cases producing urinary urgency, in others, difficulty in urination. At therapeutic dosages, fentanyl usually does not exert major effects on the cardiovascular system. However, some patients may exhibit orthostatic hypotension and fainting.

Histamine assays and skin prick 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.

Pharmacokinetics

(see graph and tables)

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

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

Following DURAGESIC® application, the skin under the system absorbs fentanyl, and a depot of fentanyl concentrates in the upper skin layers. Fentanyl then becomes available to the systemic circulation. Fentanyl concentrations increase gradually following initial DURAGESIC® application, generally leveling off between 20 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 occur between 20 and 72 hours after initial application (see Table A). Serum fentanyl concentrations achieved are proportional to the DURAGESIC® delivery rate. With continuous use, serum fentanyl concentrations continue to rise for the first 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. Patients reach and maintain a steady-state serum concentration that is determined by individual variation in skin permeability and body clearance of fentanyl.

After system removal, serum fentanyl concentrations decline gradually, falling about 50% in approximately 20-27 hours. Continued absorption of fentanyl from the skin accounts for a slower disappearance of the drug from the skin than is seen after an IV infusion, where the apparent half-life is approximately 3-12 hours.

Serum Fentanyl Concentrations

Following Single and Multiple Applications of DURAGESIC® 100 mcg/h
Fentanyl is metabolized mainly via the human cytochrome P450 3A4 isoenzyme system (CYP3A4), resulting in a 174% (range 52% - 420%) increase in fentanyl AUC. Insufficient information exists to make recommendations regarding the use of DURAGESIC® in patients with hepatic impairment and renal excretion of fentanyl. More elderly patients may be more sensitive to the active metabolites that do not contribute materially to the observed activity of the drug. Within 72 hours of IV fentanyl administration, approximately 75% of the dose is excreted in urine, mostly as metabolites. Less than 10% representing unchanged drug. Approximately 9% of the dose is recovered in the feces, primarily as metabolites. Measured clearance values for fentanyl in plasma are estimated to be between 13 and 21L/h.*

Skin, directly or after metabolism delivered transdermally. This was determined in a human keratinocyte cell assay and in clinical studies in which 90% of the dose delivered from the system was accounted for as unchanged fentanyl that appeared in the systemic circulation. The use of DURAGESIC® should be monitored by clinical evaluation, especially within the initial 24-72 hours when serum concentrations from the initial patch will peak, and following increases in dosage. DURAGESIC® should be administered to children only if they are opioid-tolerant and 2 years of age or older.

DURAGESIC® (fentanyl transdermal system) is contraindicated:
- in patients who are not opioid-tolerant
- in the management of acute pain or in patients who require opioid analgesia for a short period of time
- in the management of post-operative pain, including use after outpatient or day surgery, (e.g., tonsillectomies)
- in the management of mild pain
- in the management of intermittent pain (e.g., use on an as needed basis [prn])
- in situations of significant respiratory depression, especially in unmonitored settings where there is a lack of resuscitative equipment
- in patients who have acute or severe bronchial asthma

DURAGESIC® (fentanyl transdermal system) is contraindicated in patients who have or are suspected of having paralytic ileus.
**WARNING**: DU RAGESIC® is contraindicated in 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. Considerable pharmacology trial data in healthy adult subjects has shown that the application of heat over the DU RAGESIC® system increased mean fentanyl AUC values by 120% and mean C_max values by 61%.

Based on a pharmacokinetic model, serotonin fentanyl concentrations could theoretically increase by approximately three-fold in 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. Considerable pharmacology trial data in healthy adult subjects has shown that the application of heat over the DU RAGESIC® system increased mean fentanyl AUC values by 120% and mean C_max values by 61%.

### Dose and Administration

**DOSE AND ADMINISTRATION**

**Dose**

DU RAGESIC® patches (fentanyl transdermal system) may be used for short-term, intermittent, or around-the-clock administration and are intended for administration to the skin of the upper back. Each DU RAGESIC® patch provides a fentanyl dosage of 25 µg/h over 72 hours. Each patch contains 12 mg of fentanyl citrate, equivalent to 10 mg of fentanyl base, in a portion of the system that is covered by a patient-adhesive (e.g., Bioclusive™ or Tegaderm™).

**Application**

- The patch should be applied to a site on the upper back that is free of hair, which has good skin permeability.
- The patch should be applied to a area free of oil, sweat, or moisture.
- The patch should be applied to a site on the upper back that is free of hair, which has good skin permeability.

**Contraindications**

DU RAGESIC® is contraindicated in patients with a history of opioid allergy, including a history of anaphylaxis, or who are hypersensitive to the active ingredient or any other component of DU RAGESIC®. DU RAGESIC® patches are contraindicated in patients with a known history of opioid addiction, or in those who are susceptible to overdose or abuse. DU RAGESIC® patches are also contraindicated in patients with a history of drug abuse, or in patients with a known history of liver disease, or in patients with a history of renal disease.

**Warnings and Precautions**

- **Drug Interactions:** DU RAGESIC® patches contain fentanyl, an opioid pain medicine similar to morphine, hydromorphone, methadone, oxycodone, and oxymorphone. Drug interactions may occur, resulting in serious injury or death.
- **Overdose:** DU RAGESIC® patches contain fentanyl, an opioid pain medicine similar to morphine, hydromorphone, methadone, oxycodone, and oxymorphone. Drug interactions may occur, resulting in serious injury or death.
- **Misuse, Abuse, and Diversion of Opioids:** Fentanyl is an opioid agonist of the morphine-type. Such drugs are sought by drug abusers and people with addiction disorders and are subject to criminal diversion. Fentanyl can be abused in a manner similar to other opioids, legal or illicit. This should be considered when prescribing or dispensing DU RAGESIC® in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse, or diversion.

### Drug Interactions

**Bioavailability:** The absorption of DU RAGESIC® is influenced by several factors, including the amount of active fentanyl remaining in DU RAGESIC® after use as directed. Accidental or deliberate application or ingestion by a child or adolescent will cause respiratory depression that could result in death.

**Misuse, Abuse, and Diversion of Opioids:** Fentanyl is an opioid agonist of the morphine-type. Such drugs are sought by drug abusers and people with addiction disorders and are subject to criminal diversion. Fentanyl can be abused in a manner similar to other opioids, legal or illicit. This should be considered when prescribing or dispensing DU RAGESIC® in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse, or diversion.

**Abuse and Diversion:** DU RAGESIC® is an opioid product that is subject to abuse and diversion. Patients should be advised to store DU RAGESIC® in a location that is inaccessible to children and others for whom DU RAGESIC® was not prescribed. A considerable amount of active fentanyl remains in DU RAGESIC® even after use as directed. Accidental or deliberate application or ingestion by a child or adolescent will cause respiratory depression that could result in death.

**Cardiac Disease:** Fentanyl may produce bradycardia. Fentanyl should be administered with caution to patients with bradycardia or sinus bradyarrhythmias.

**Hepatic or Renal Disease:** Patients should be advised to consult with their healthcare provider before taking DU RAGESIC® in patients with impaired renal or hepatic function. If the drug is used in these patients, it should be used with caution because of the hepatic metabolism and renal excretion of fentanyl.

**Use in Pancreatitis/Biliary Tract Disease:** DU RAGESIC® may cause spasm of the sphincter of Oddi and should be used with caution in patients with biliary tract disease, including acute pancreatitis. Opioids like DU RAGESIC® may cause increases in bilirubin and alkaline phosphatase due to mu-opioid receptor activation.

**Tolerance:** Tolerance is a state of adaptation in which exposure to a drug induces changes that result in a diminution of one or more of the drug’s effects over time. Tolerance may occur to both the desired and undesired effects of drugs, and may develop at different rates for different effects.

**Physical Dependence:** Physical dependence is a state of adaptation that is manifested by an opioid specific withdrawal syndrome that can be produced by abrupt cessation, rapid dose reduction, decreasing blood concentration of the drug, and/or administration of an antagonist. The opioid abstinence or withdrawal syndrome is characterized by some or all of the following: restlessness, lacrimation, rhinorrhea, yawning, perspiration, chills, piloerection, myalgia, mydriasis, irritability, anxiety, back pain, insomnia, nausea, vomiting, diarrhea, or increased bowel pressure, respiratory rate, or heart rate. In general, opioids should not be abruptly discontinued because of the risk of physical dependence and potentially dangerous withdrawal effects.

**DOSE AND ADMINISTRATION – Discontinuation of DU RAGESIC®:**

**Ambulatory Patients:** Strong opioid analgesics impair the mental or physical abilities required for the performance of potentially hazardous tasks, such as driving a car or operating machinery. Patients should be advised to discontinue DU RAGESIC® without delay if they have been given DU RAGESIC® should not drive or operate dangerous machinery unless they are tolerant to the effects of the drug.

**Information for Patients:** Patients and their caregivers should be provided with a Medication Guide each time DU RAGESIC® is prescribed because new information may be available.

**Patients receiving DU RAGESIC® patches should be given the following instructions by the physician:**

1. Patients should be advised that DU RAGESIC® patches contain fentanyl, an opioid pain medicine similar to morphine, hydromorphone, methadone, oxycodone, and oxymorphone. Drug interactions may occur, resulting in serious injury or death.
2. Patients should be advised that each DU RAGESIC® patch may be worn continuously for 72 hours, and that each patch should be applied to a different skin site after removal of the previous transdermal patch.
3. Patients should be advised that DU RAGESIC® patches should be applied to intact, non-irritated, and non-inflamed skin. If the skin surface is the chest, back, flank, or upper arm. Additionally, patients should be advised of the following:

   - In young children or persons with cognitive impairment, the patch should be put on the upper back to lower the chances that the patch will be removed and placed in the mouth.
   - Have the skin application site be clipped (not shaved) prior to patch application.
   - If the site of DU RAGESIC® application must be cleansed prior to application of the patch, do so with clear water.
   - Do not use soaks, 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.
4. Patients should be advised that DU RAGESIC® should be applied immediately upon removal from the sealed pouch and after removal of the protective liner. Additionally the patient should be advised of the following:
   - The DU RAGESIC® patch should not be used if the pouch seal is broken, or if the patch is cut, damaged, or changed in any way.
5. Patients should be advised that the dose of DU RAGESIC® or the number of patches applied to the patient should never be changed without the prescribing healthcare provider’s instruction.
6. Patients should be advised that while wearing the patch, they should avoid exposing the DU RAGESIC® application site surrounding area to direct external heat sources, such as:
   - heating pads,
   - electric blankets,
   - sunbathing,
   - heat or tanning lamps,
   - saunas,
   - hot tubs or hot baths, and
   - heated water beds, etc.
7. Patients should also be advised of a potential for temperature-dependent increases in fentanyl release that can occur in an area of overheating, for example, patients who develop a high fever or increased body temperature due to strenuous exertion while wearing the patch should contact their physician.
8. Patients should be advised that if they experience problems with adhesion of the DU RAGESIC® patch, they may tear the edges of the patch with first aid tape. If problems with adhesion persist, patients should notify the patch with a transparent adhesive film dressing (e.g., Bioclusive™ or Tegaderm™).
9. Patients should be advised that if the patch falls off by 72 hours a new patch may be applied to a different skin site, and:
10. Patients should be advised to fold (so that the adhesive side adheres to itself) and immediately flush down the toilet used DU RAGESIC® patches after removal from the skin.
11. Patients should be advised that DU RAGESIC® may impair mental and/or physical ability required for the performance of potentially hazardous tasks (e.g., driving, operating machinery).
12. Patients should be advised to refrain from any potentially dangerous activity when starting on DU RAGESIC® or when their dose is being adjusted, until it is established that they have not been adversely affected.
13. Patients should be advised that DU RAGESIC® should not be combined with alcohol or other CNS depressants (e.g. sleep medications, tranquilizers) because dangerous additive effects may occur, resulting in serious injury or death.
the body weight of the live fetuses at the high dose, which may be attributed to maternal toxicity.

DU RAGESIC®

Under the conditions of the assay, there was no evidence for fentanyl induced adverse effects on delivery time in the 0.03 mg/kg/day group. There was no clear evidence of teratogenicity noted.

Pregnancy – Pregnancy Category C

The potential effects of fentanyl on embryo-fetal development were studied in the rat, mouse, and microosmotic minipumps did not produce any evidence of teratogenicity (the high dose is approximately 2.5 times the daily human dose admistered by a 100 mcg/hr patch on a m g/m 2 basis).

DURAGESIC® (Fentanyl Transdermal System)

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 high-dose are 0.4 and 1.6 times the daily human dose administered by a 100 mcg/hr patch on a mg/m 2 basis.

Labor and Delivery

Fentanyl readily crosses the placenta to the fetus; therefore, DURAGESIC® is not recommended for analgesia during labor and delivery.

Nursing Mothers

Fentanyl is secreted in human milk; therefore, DURAGESIC® is not recommended for use in nursing women because of the possibility of effects in their infants.

Pediatric Use

The duration of DU RAGESIC® was evaluated in three open-label trials in 291 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 mcg/day of oral morphine or an equianalgesic dose of another opioid. Initiation of DU RAGESIC® therapy in pediatric patients taking less than 60 mcg/day of oral morphine or an equianalgesic dose of another opioid resulted in analgesia in 78% of the patients who were evaluated in controlled clinical trials. Approximately 90% of the total daily opioid requirement (DU RAGESIC® plus rescue medication) was provided by DU RAGESIC®.

DU RAGESIC® was not studied in children under 2 years of age.

DU RAGESIC® should be administered to children only if they are opioid-tolerant and 2 years of age or older (see DOSAGE AND ADMINISTRATION and BOX WARNING).

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

Geriatric Use

In in vitro 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 adverse effects of respiratory depression. Elderly patients demonstrated a lower respiratory depression threshold when compared to young adult subjects, although peak serum concentrations tended to be lower and more variable in elderly subjects.

Respiratory depression is the chief hazard in elderly or debilitated patients, usually following large initial doses in non-tolerant patients, or when opioids are given in conjunction with other agents that depress respiration.

DU RAGESIC® should be used with caution in elderly, cachetic, or debilitated patients as they may have altered pharmacokinetics due to poor fat stores, muscle wasting or altered clearance (see BOX WARNING, CLINICAL PHARMACOLOGY).

ADVERSE REACTIONS

In post-marketing experience, deaths from hypoventilation due to use of DU RAGESIC® transdermal system have been reported (see BOX WARNING and CONTRAINDICATIONS).

The potential effects of fentanyl on embryo-fetal development include increased incidence of tumors at subcutaneous doses up to 33 µg/kg/day in male rats or 100 µg/kg/day in female rats. In the in vitro study, male rats were treated with fentanyl (0.01, 0.05, 0.1, 0.4 mg/kg/day) via continuous intravenous infusion for 14 days prior to mating until day 16 of pregnancy; male rats were not treated. Analysis of fertility parameters in both studies indicated that an intravenous dose of 1 mg/kg/day or the female alone (0.05 mg/kg/day) had no effects on fertility. This dose is approximately 1.6 times the daily human dose administered by a 100 mcg/hr patch on a m g/m 2 basis. In a separate study, daily total basal dose of fentanyl was shown to impair fertility in rats when given in intravenous doses of 0.3 times the human dose for a period of 12 days.

Pregnancy

Pregnancy Category C

No epidemiological studies of congenital anomalies in infants born to women treated with fentanyl during pregnancy have been reported.

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 (0.1, 10, 100, or 500 µg/kg) to pregnant Sprague-Dawley rats from day 7 to 21 via implanted microosmotic 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/m 2 basis). In a separate study, gestation 6 to 18 observed evidence of embryotoxicity 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 (0.025, 0.05, 0.4 mg/kg via intravenous infusion from day 6 to day 18 of pregnancy. Fentanyl produced a slight decrease in the body weight of the live fetuses at the high dose, which may be attributed to maternal toxicity. Under the conditions of the assay, there was no evidence for fentanyl induced adverse effects on embryo-fetal development at doses up to 0.4 mg/kg (approximately 3 times the daily human dose administered by a 100 mcg/hr patch on a mg/m 2 basis).

There are adequate and well-controlled studies in pregnant women. DURAGESIC® should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nontarget Tissue Effects

Chronic maternal treatment with fentanyl during pregnancy has been associated with transient respiratory depression, behavioral changes, or seizures characteristic of neonatal abstinence. Patients receiving DU RAGESIC® are recommended for analgesia during labor and delivery.
**DURAGESIC®** (Fentanyl Transdermal System)

The following adverse effects have been reported in less than 1% of the 510 adult post-operative and cancer patients studied:

**Cardiovascular:** bradycardia

**Digestive:** abdominal distension

**Nervous:** headache, vertigo, stupor, hypotonia, depersonalization, hostility

**Respiratory:** tachy- or bradypnea, asthma, respiratory disorder

**Skin and Appendages:** exfoliative dermatitis, pustules

**Special Senses:** amblyopia

**Urogenital:** bladder pain, oliguria, urinary frequency

**Post-Marketing Experience - Adults**

The following adverse reactions have been reported in association with the use of DURAGESIC® and not reported in the pre-marketing adverse reactions section above.

**Body as a Whole:** edema

**Cardiovascular:** tachycardia

**Metabolic and Nutritional:** weight loss

**Special Senses:** blurred vision

**Urogenital:** decreased libido, impotence, ejaculatory difficulty

**DRUG ABUSE AND ADDICTION**

DURAGESIC® contains a high concentration of fentanyl, a potent Schedule II opioid agonist. Schedule II opioid substances, which include hydrocodone, methadone, morphine, oxycodone, and oxymorphone, have the highest potential for abuse and risk of fatal overdose due to respiratory depression. Fentanyl, like morphine and other opioids used in analgesia, can be abused and is subject to criminal diversion.

The high content of fentanyl in the patches (DURAGESIC®) may be a particular target for abuse and diversion.

Addiction is a primary, chronic, neurobiologic disease with genetic, psychosocial, and environmental factors influencing its development and manifestations. It is characterized by behaviors that include one or more of the following: impaired control over drug use, compulsive use, continued use despite harmful consequences, and addiction. Drug addiction is a treatable, chronic, relapsing brain disease, not a choice. Drug addiction, unlike physiological dependence, continues despite harmful consequences.

**OVERDOSAGE**

**Clinical Manifestation**

The manifestations of fentanyl overdose are an extension of its pharmacologic actions with the most serious effect being hypotension.

**Treatment**

For the management of hypotension, immediate countermeasures include removing the DURAGESIC® (fentanyl transdermal system) system and physically or verbally stimulating the patient. These actions can be followed by administration of a specific narcotic antagonist such as naloxone. The duration of hypotension following an overdose may be longer than the effects of the narcotic antagonist’s action (the half-life of naloxone ranges from 30 to 81 minutes). The interval between multiple doses should be chosen carefully because of the possibility of re-narcotization after system removal; repeated administration of naloxone may be necessary. Reversal of respiratory depression may not be evident in all patients and the release of endogenous opioids may persist. Always ensure a patent airway is established and maintained, administer oxygen and assist or control respiration as indicated and use an oropharyngeal airway or endotracheal tube if necessary. Adequate body temperature should be maintained.

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

**DOSAGE AND ADMINISTRATION**

**Special Precautions**

DURAGESIC® contains a high concentration of a potent Schedule II opioid agonist, fentanyl. Schedule II opioid substances which include fentanyl, hydrocodone, methadone, morphine, oxycodone, and oxymorphone have the highest potential for abuse and associated risk of fatal overdose due to respiratory depression. Fentanyl can be abused and is subject to criminal diversion. The high content of fentanyl in the patches (DURAGESIC®) may be a particular target for abuse and diversion.

**DURAGESIC®** patches are intended for transdermal use (on intact skin) only. The DURAGESIC® patch should not be used if the pouch seal is broken, or the patch is cut, damaged or applied in any way.

Each DURAGESIC® patch may be worn continuously for 72 hours. The next patch should be applied to a different skin site after removal of the previous transdermal system.

If problems with adhesion of the DURAGESIC® patch occur, the edges of the patch may be taped with first aid tape or with hypoallergenic adhesive tape, which may be overlapped with a transparent adhesive film dressing (e.g., Bioclusive™ or Tegaderm®).

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.

**DURAGESIC®** is only for use in patients who are already tolerant to opioid therapy of comparable potency. Use in non-opioid tolerant patients may lead to fatal respiratory depression. DURAGESIC®® dose when converting patients from another opioid medication can result in fatal overdose with the first dose. Due to the mean half-life of approximately 20-27 hours, patients who are thought to have had a serious adverse event, including overdose, should be monitored for at least 24 hours.

The concomitant use of DURAGESIC® with all cytochrome P450 3A4 inhibitors (such as ritonavir, ketoconazole, itraconazole, lovastatin, clarithromycin, nefazodone, amiodarone, ampicillin, azithromycin, diltiazem, erythromycin, fluconazole, fosamprenavir, grapefruit juice, and 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. Patients receiving DURAGESIC®® and any CYP3A4 inhibitor should be carefully monitored for an extended period of time and dosage adjustments should be made if warranted (see BOX WARNING, CLINICAL PHARMACOLOGY – Drug Interactions, WARNINGS and PRECAUTIONS for further information).

**Pediatric Patients**

**DRUG ABUSE AND ADDICTION**

Pediatric patients converting to DURAGESIC® with a 25 mcg/h patch should be opioid-tolerant and managed using the same schedule described in Table C, and method of titration described below are recommended in opioid-tolerant pediatric patients 2 years of age with chronic pain (see PRECAUTIONS – Pediatric Use).

Respiratory depression is the chief hazard in elderly or debilitated patients, usually following large doses or rapid parenteral administration in non-opioid-tolerant patients, or when opioids are given in conjunction with other drugs that depress respiration.

**DRUG ABUSE AND ADDICTION** should be used with caution in elderly, cachectic, or debilitated patients as they may have altered pharmacokinetics due to age, impaired hepatic or renal function, or altered clearance (see CLINICAL PHARMACOLOGY – Special Populations, Geriatric Use).

**General Principles**

DURAGESIC®® is indicated for management of persistent, moderate to severe chronic pain that:

- requires continuous, around-the-clock opioid administration for an extended period of time
- cannot be managed by other means such as non-steroidal analgesics, opioid combination products, or immediate-release opioids.

**Precautions**

DURAGESIC® should be used in patients who are already receiving opioid therapy, who have demonstrated opioid tolerance, and who require a total daily dose at least equivalent to DURAGESIC® 25 mcg/h. Patients who are considered opioid-tolerant are those who have been taking, for a week or longer, at least 60 mg of morphine daily, or at least 30 mg of oral hydromorphone daily, or at least 8 mg oral hydromorphone daily, or an equianalgesic dose of another opioid.

Because serious or life-threatening hyperventilation could occur, DURAGESIC® fentanyl transdermal system is contraindicated in patients who:

- are not opioid-tolerant
- in the management of acute pain or in patients who require opioid analgesia for a short period
- in the management of post-operative pain, including use after out-patient or day surgeries (e.g., tonsillectomies)
- in the management of mild pain
- in the management of intermittent pain (e.g., use on an as needed basis [prn])

(See CONTRAINDICATIONS for further information.)

**Safety of DURAGESIC® has not been established in children under 2 years of age.**

DURAGESIC® should be administered to children only if they are opioid-tolerant and 2 years of age (see PRECAUTIONS – Pediatric Use).

Prescribers should individualize treatment using a progressive plan of pain management such as outlined by the World Health Organization, the Agency for Health Research and Quality, the American Pain Society, the State Medical Board of Ohio, the American Academy of Pediatrics, and the Department of Health and Human Services.

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

DURAGESIC® should be applied immediately upon removal from the sealed package. Do not use if the pouch seal is broken. Do not alter the patch (e.g., cut) in any way prior to application and do not use cut or damaged patches.

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

DURAGESIC® should be kept out of the reach of children. Used patches should be folded so that the adhesive side of the patch adheres to itself, then the patch should be flushed down the toilet immediately upon removal. Patients should dispose of any patches remaining from a prescription as soon as they are no longer needed. Unused patches should be removed from their pouches, folded so that the adhesive side of the patch adheres to itself, and flushed down the toilet.

**Dose Selection**

Doses should be individualized based upon the status of each patient and should be assessed at regular intervals. When DURAGESIC® or other transdermal systems are used as part of a combination opioid regimen, the dosage should be reduced if the dosage is determined to be excessive (e.g., more than once daily).

**DURAGESIC®® is only for use in patients who are already tolerant to opioid therapy of comparable potency. Use in non-opioid tolerant patients may lead to fatal respiratory depression.**

In selecting an initial DURAGESIC® dose, attention should be given to 1) the daily dose, potency, and characteristics of the opioid the patient has been taking previously (e.g., whether it is a pure agonist-antagonist, 2) the reliability of the relative potency estimates used to calculate the DURAGESIC® dose needed (potency estimates may vary with the route of administration), 3) the degree of opioid tolerance and 4) the general condition and medical status of the patient. Each patient should be maintained at the lowest dose providing acceptable pain control.

**Initial DURAGESIC® Dose Selection**

Initial DURAGESIC® dose when converting patients from another opioid medication can result in fatal overdose with the first dose. Due to the mean half-life of approximately 20-27 hours, patients who are thought to have had a serious adverse event, including overdose, will require monitoring and treatment for at least 24 hours.

There has been no systematic evaluation of DURAGESIC®® as an initial opioid analgesic in the management of chronic pain, since most patients in the clinical trials were converted to DURAGESIC® from other narcotics. The efficacy of DURAGESIC® 12 mcg/h as an initiating dose has not been determined. In addition, the use of opioid supplementation or titration to a standard dose (e.g., not more than 24 hours) of DURAGESIC® for the treatment of chronic pain is not recommended. Therefore, DURAGESIC® should be used only in patients who are opioid-tolerant.

To convert adult and pediatric patients from oral or parenteral opioids to DURAGESIC®, use Table C.
NOTE: In clinical trials, these ranges of daily oral morphine doses were used as a basis for conversion to DURAGESIC®.

1. Table E should not be used to convert from DURAGESIC® to other therapies because this conversion to DURAGESIC® is conservative. Use of Table E for conversion to other analgesic therapies can overestimate the dose of the new agent. Overdosage of the new analgesic agent is possible (see DOSAGE AND ADMINISTRATION - Discontinuation of DURAGESIC®).

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

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

During the initial application of DURAGESIC®, patients should use short-acting analgesics as needed until analgesic efficacy with DURAGESIC® is attained. Thereafter, some patients may require periodic supplemental doses of other short-acting analgesics for “breakthrough” pain.

Dose Titration

The recommended initial DURAGESIC® dose based upon the daily oral morphine dose is conservative, and 50% of patients are likely to require a dose increase after initial application of DURAGESIC®. The initial DURAGESIC® dose may be increased after 3 days based on the daily dose of supplemental opioid analgesics required by the patient in the second or third day of the initial application (see graph in CLINICAL PHARMACOLOGY).

Physicians are advised that it may take up to 6 days after increasing the dose of DURAGESIC® for the patient to reach equilibrium on the new dose (see graph in CLINICAL PHARMACOLOGY).

Therefore, patients should wear a higher dose through two applications before any further increase in dosage is made on the basis of the average daily use of a supplemental analgesic.

Appropriate dosage increments should be based on the daily dose of supplementary opioids, using the ratio of 45 mg/24 hours of oral morphine to a 12.5 mcg/h increase in DURAGESIC® dose. DURAGESIC®-12 delivers 12.5 mcg/h of fentanyl.

Discontinuation of DURAGESIC®

To convert patients from another opioid, remove DURAGESIC® and titrate the dose of the new analgesic based upon the patient’s report of pain until adequate analgesia has been attained. Upon system removal, 17 hours or more are required for a 50% decrease in serum fentanyl concentrations. Opioid withdrawal symptoms (such as nausea, vomiting, diarrhea, anxiety, and shivering) are possible in some patients after conversion or dose adjustment. For patients requiring discontinuation of opioids, a gradual downward titration is recommended since it is not known at what dose level the opioid may be discontinued without producing the signs and symptoms of abrupt withdrawal.

Overdose of the new analgesic agent is possible.

HOW SUPPLIED

DURAGESIC® (fentanyl transdermal system) is supplied in cartons containing 5 individually packaged systems. See chart for information regarding individual systems.

Safety and Handling

DURAGESIC® is supplied in sealed transdermal systems which pose little risk of exposure to health care workers. Do not use a DURAGESIC® patch if the pouch seal is broken or the patch is cut, damaged, or changed in any way.

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

Store in original unopened pouch. Store up to 25°C (77°F); excursions permitted to 15 - 30°C (59 - 86°F). Apply immediately after removal from individually sealed pouch. Do not use if the pouch seal is broken. For transdermal use only.

Bioavailability® is a trademark of Ethicon, Inc.

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A schedule II narcotic. DEA order form required.

Manufactured by: ALZA Corporation
Vacaville, CA 95688

Manufactured for: PriCara®, Division of Ortho-McNeil-Janssen Pharmaceuticals, Inc.
Raritan, NJ 08869

Division of Ortho-McNeil-Janssen Pharmaceutica, Inc.

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DURAGESIC®
(Fentanyl Transdermal System)