Janssen, L.P.

# IMPORTANT DRUG WARNING

Dear Healthcare Professional, June 2005

Janssen, L.P., would like to inform you of important changes in the prescribing information for DURAGESIC® (fentanyl transdermal system), CII. The DURAGESIC prescribing information will now include important safety information in the following areas of the labeling: Use Only in Opioid-Tolerant Patients, Misuse, Abuse and Diversion, Hypoventilation (Respiratory Depression), Interactions with CYP3A4 Inhibitors, Damaged or Cut Patches, Accidental Exposure to Fentanyl, Chronic Pulmonary Disease, Head Injuries and Intracranial Pressure, Interactions with Other CNS Depressants, and Interactions with Alcohol and Drugs of Abuse. The changes reflect FDA's efforts to harmonize labeling for controlled-release CII products as well as a heightened awareness of safety issues associated with opioids in general, such as abuse, misuse and diversion.

The Boxed Warning and the WARNINGS sections of the prescribing information have been updated and are presented in their entirety, starting below. Underlining and bolding have been added for the purpose of prominence and do not necessarily suggest new text. These warnings are also reflected in updates to the CLINICAL PHARMACOLOGY, CONTRAINDICATIONS, PRECAUTIONS, and DOSAGE AND ADMINISTRATION sections of the prescribing information.

**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®) may be a particular target for abuse and diversion.**

**DURAGESIC® is indicated for management of <u>persistent</u>, 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**

1125 TRENTON-HARBOURTON ROAD
POST OFFICE BOX 200
TITUSVILLE, NEW JERSEY 08560-0200
(609) 730-2000

**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 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 oxycodone daily, or at least 8 mg of oral hydromorphone daily or an equianalgesic dose of another opioid.**

**Because serious or life-threatening hypoventilation 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)]**

**(See CONTRAINDICATIONS for further information.)**

**Since the peak fentanyl levels occur between 24 and 72 hours of treatment, prescribers should be aware that serious or life threatening hypoventilation may occur, even in opioid-tolerant patients, during the initial application period.**

**The concomitant use of DURAGESIC® with potent cytochrome P450 3A4 inhibitors (ritonavir, ketoconazole, itraconazole, troleandomycin, clarithromycin, nelfinavir, and nefazodone) 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 potent CYP3A4 inhibitors 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. Due to the mean elimination half-life of 17 hours of DURAGESIC®, patients who are 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 or 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 abuse may still be**

**appropriately treated with modified-release opioid formulations; however, these patients will require intensive monitoring for signs of misuse, abuse, or addiction.**

**DURAGESIC® patches are intended for transdermal use (on intact skin) only. Using damaged or cut DURAGESIC® patches can lead to the rapid release of the contents of the DURAGESIC® patch and absorption of a potentially fatal dose of fentanyl.**

.

**WARNINGS**

**DURAGESIC® patches are intended for transdermal use (on intact skin) only. Using damaged or cut DURAGESIC® patches can lead to the rapid release of the contents of the DURAGESIC® patch and absorption of a potentially fatal dose of fentanyl.**

**The safety of DURAGESIC® (fentanyl transdermal system) 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. The mean elimination half-life of DURAGESIC® is 17 hours.** Therefore, patients who have experienced serious adverse events, including overdose, will require monitoring for at least 24 hours after DURAGESIC® removal since serum fentanyl concentrations decline gradually and reach an approximate 50% reduction in serum concentrations 17 hours after system removal.

DURAGESIC® should be prescribed only by persons knowledgeable in the continuous administration of potent opioids, in the management of patients receiving potent opioids for treatment of pain, and in the detection and management of hypoventilation including the use of opioid antagonists.

**All patients and their caregivers should be advised to avoid exposing the DURAGESIC® application site to direct external heat sources, such as heating pads or electric blankets, heat lamps, saunas, hot tubs, and heated water beds, etc., while wearing the system. There is a potential for temperature-dependent increases in fentanyl released from the system resulting in possible overdose and death (see PRECAUTIONS - Patients with Fever/External Heat).**

Death and other serious medical problems have occurred when people were accidentally exposed to DURAGESIC®. Examples of accidental exposure include transfer of a DURAGESIC® patch from an adult's body to a child while hugging, accidental sitting on a patch and possible accidental exposure of a caregiver's skin to the medication in the patch while the caregiver was applying or removing the patch.

Placing DURAGESIC® 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.

**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 DURAGESIC® in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse or diversion.

DURAGESIC® has been reported as being abused by other methods and routes of administration. These practices will result in uncontrolled delivery of the opioid and pose a significant risk to the abuser that could result in overdose and death (see **WARNINGS** and **DRUG ABUSE AND ADDICTION**).

Concerns about abuse, addiction and diversion should not prevent the proper management of pain. However, all patients treated with opioids require careful monitoring for signs of abuse and addiction, since use of opioid analgesic products carries the risk of addiction even under appropriate medical use.

Healthcare professionals should contact their state professional licensing board or state controlled substances authority for information on how to prevent and detect abuse or diversion of this product.

**Hypoventilation (Respiratory Depression)**
Serious or life-threatening hypoventilation may occur at any time during the use of DURAGESIC® especially during the initial 24-72 hours following initiation of therapy and following increases in dose.

Because significant amounts of fentanyl are absorbed from the skin for 17 hours or more after the patch is removed, hypoventilation may persist beyond the removal of DURAGESIC®. Consequently, patients with hypoventilation should be carefully observed for degree of sedation and their respiratory rate monitored until respiration has stabilized.

The use of concomitant CNS active drugs requires special patient care and observation.

Respiratory depression is the chief hazard of opioid agonists, including fentanyl the active ingredient in DURAGESIC®. Respiratory depression is more likely to occur in elderly or debilitated patients, usually following large initial doses in non-tolerant patients, or when opioids are given in conjunction with other drugs that depress respiration.

Respiratory depression from opioids is manifested by a reduced urge to breathe and a decreased rate of respiration, often associated with the “sighing” pattern of breathing (deep breaths separated by abnormally long pauses). Carbon dioxide retention from opioid-induced respiratory depression can exacerbate the sedating effects of opioids. This makes overdoses involving drugs with sedative properties and opioids especially dangerous.

DURAGESIC® should be used with extreme caution in patients with significant chronic obstructive pulmonary disease or cor pulmonale, and in patients having a substantially decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression. In such patients, even usual therapeutic doses of DURAGESIC® may decrease respiratory drive to the point of apnea. In these patients, alternative non-opioid analgesics should be considered, and opioids should be employed only under careful medical supervision at the lowest effective dose.

**Chronic Pulmonary Disease**
Because potent opioids can cause serious or life-threatening hypoventilation, DURAGESIC® should be administered with caution to patients with pre-existing medical conditions predisposing them to hypoventilation. In such patients, normal analgesic doses of opioids may further decrease respiratory drive to the point of respiratory failure.

**Head Injuries and Increased Intracranial Pressure**
DURAGESIC® should not be used in patients who may be particularly susceptible to the intracranial effects of $CO_2$ retention such as those with evidence of increased intracranial pressure, impaired consciousness, or coma. Opioids may obscure the clinical course of patients with head injury. DURAGESIC® should be used with caution in patients with brain tumors.

**Interactions with other CNS Depressants**
The concomitant use of DURAGESIC® (fentanyl transdermal system) with other central nervous system depressants, including but not limited to other opioids, sedatives, hypnotics, tranquilizers (e.g., benzodiazepines), general anesthetics, phenothiazines, skeletal muscle relaxants, and alcohol, may cause respiratory depression, hypotension, and profound sedation or potentially result in coma. When such combined therapy is contemplated, the dose of one or both agents should be significantly reduced.

**Interactions with Alcohol and Drugs of Abuse**
Fentanyl may be expected to have additive CNS depressant effects when used in conjunction with alcohol, other opioids, or illicit drugs that cause central nervous system depression.

**Interactions with CYP3A4 Inhibitors**
**The concomitant use of DURAGESIC® with potent cytochrome P450 3A4 inhibitors (ritonavir, ketoconazole, itraconazole, troleandomycin, clarithromycin, nelfinavir, and nefazodone) 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 potent CYP3A4 inhibitors 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, PRECAUTIONS and DOSAGE AND ADMINISTRATION for further information.)**

As there are additional changes outside of those made to the Boxed Warning and WARNINGS sections, we urge you to thoroughly review the accompanying full prescribing information for DURAGESIC.

Janssen, L.P., remains committed to providing you with the most current product information on all of our products to help in the management of your patients. As always, we request that serious adverse events be reported to Janssen at 1-800-JANSSEN (800-526-7736), or to the FDA MedWatch program by phone (1-800-FDA-0188), by fax (1-800-FDA-0178), or by e-mail (www.fda.gov/medwatch).

For additional information about DURAGESIC, or any other Janssen product, please call 1-800-JANSSEN (800-526-7736) from 9AM to 5PM EST, Monday through Friday.

Sincerely,

Norman Rosenthal, MD
Vice President, Medical Affairs