May 13, 2011

Stacy Handley
9 Richland Medical Park
Columbia, SC 29203
US

Dear Ms. Handley:

Thank you for contacting Medical Information and Services regarding DURAGESIC® (fentanyl transdermal system). The enclosed information has been supplied to you in response to your unsolicited request and is not intended as an endorsement of any usage not contained in the prescribing information.

Response(s):

- DURAGESIC - Use with an Occlusive Dressing
- DURAGESIC - Material Safety Data Sheet (MSDS)—Please see this enclosed document to address your inquiry pertaining to whether the drug is in a flammable base.
- DURAGESIC - Effect of Hyperbaric Treatment on Duragesic Release
- DURAGESIC - Stability - Extreme Heat

For complete information, please refer to the enclosed full DURAGESIC Prescribing Information, including the following sections: **BOXED WARNING(S), INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS, and ADVERSE REACTIONS**. If you have any additional questions, please contact us via:

- Phone: 1-800-526-7736 (Monday through Friday, 9:00 a.m. through 5:00 p.m. ET)
- Web Site: www.omjsamedicalinformation.com

To report a possible adverse event or product quality complaint, please call the Customer Communications Center immediately, at 1-800-526-7736.

Sincerely,

LouAnn Lalumia, BS, RD
Senior Therapeutic Specialist
Medical Information and Services
Medical Information

Inquiry #: 1-1202051321

Enclosure(s): See page 10 for a list of enclosure(s).

DURAGESIC® (fentanyl transdermal system)

The following information is provided because of your specific unsolicited request and is not intended as an endorsement of any usage not contained in the Prescribing Information. For complete information, please refer to the enclosed full Prescribing Information, including the following sections: **BOXED WARNING(S), INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS, and ADVERSE REACTIONS**.

SUMMARY:

DURAGESIC - Use with an Occlusive Dressing

- Patients should be advised that if they experience problems with adhesion of the DURAGESIC® patch, they may tape the edges of the patch with first aid tape. If problems with adhesion persist, patients may overlay the patch with a transparent adhesive film dressing (e.g., Bioclusive™ or Tegaderm™).[1]
- Patients should be advised that if the patch falls off before 72 hours, dispose of it by folding it in half and flushing the patch down the toilet. A new patch may be applied to a different skin site.[1]

DURAGESIC - Material Safety Data Sheet (MSDS)

- Please find enclosed the MSDS for DURAGESIC®.

DURAGESIC - Effect of Hyperbaric Treatment on Duragesic Release

- The authors of an in vitro study on the release of fentanyl following hyperbaric treatment with 100% oxygen noted a trend of an increased release of fentanyl from patches following the first hyperbaric treatment.[2]
- Shirley et al conducted an in vitro study on the release of fentanyl following hyperbaric treatment with 100% oxygen, which was significantly higher ($p<0.05$) than from untreated patches at 37, 39, and 42°C.[3]

DURAGESIC - Stability - Extreme Heat

- A MEDLINE and an internal database literature search (1990 - July 2009) failed to identify any citations relevant to the effects of extreme heat on the stability of DURAGESIC®.
- DURAGESIC® (Matrix formulation) was found to be stable for six months when stored at 40° C / 75% relative humidity or 30° C. Properties of DURAGESIC® were also found to be unaffected in cycling studies from 4° C to 40° C to 4° C over two weeks and from 25° C to -10° C (freeze-thaw) over 24 hours for three days.[4]
- Stability studies have found DURAGESIC® (Reservoir formulation) to have met product specifications when stored at either 30° C (86° F) for 12 months or 40° C (104° F) for 1 week followed by 25° C (77° F) for 12 months. Physical changes begin to occur above 40° C. It is recommended that systems stored beyond the above parameters be discarded.[4]
- Do not store above 77°F (25°C). Apply immediately after removal from individually sealed package. Do not use if the seal is broken.[1]

DURAGESIC - Use with an Occlusive Dressing

BOX WARNING[1]

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®) may be 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 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® 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 generally occur between 20 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 all cytochrome P450 3A4 inhibitors (such as ritonavir, ketoconazole, itraconazole, troleandomycin, clarithromycin, nelfinavir, 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 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 and 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 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. Do not use a DURAGESIC® patch if the 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, heat or tanning 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 exertion should be monitored for opioid side effects and the DURAGESIC® dose should be adjusted if necessary.

PRESCRIBING INFORMATION

Please refer to the following sections of the Full Prescribing Information which are relevant to your inquiry: DOSAGE AND ADMINISTRATION, PRECAUTIONS

DOSAGE AND ADMINISTRATION[1]

If problems with adhesion of the DURAGESIC® patch occur, the edges of the patch may be taped with first aid tape. If problems with adhesion persist, the patch may be overlayed with a transparent adhesive film dressing (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.

AVAILABLE LITERATURE

A MEDLINE and an internal database literature search (1990 – August 2009) did not yield any relevant citations regarding the use of DURAGESIC® with an occlusive dressing. An additional search of Ovid MEDLINE®, Derwent Drug File, and EMBASE from September 2009–April 2011 was done to capture any additional literature published during that date range. No relevant citations were identified.

Material Safety Data Sheet (MSDS)

The Occupational Safety and Health Administration (OSHA) has a regulation requiring that Material Safety Data Sheets (MSDS) for pharmaceutical products be available at all health care provider sites (pharmacies, hospitals, doctor's offices, clinics, etc). The MSDS contains information related to safe handling of the product (ie. how to clean up a large spill, what to do in the event of fire, what precautions to take when handling the product, etc).

Enclosed is the Material Safety Data Sheet (MSDS) you requested for DURAGESIC® (fentanyl transdermal system) CII.[5]

DURAGESIC - Effect of Hyperbaric Treatment on Duragesic Release

PUBLISHED LITERATURE

A MEDLINE literature search and a search of an internal database (1992 - August 2009) identified two citations on the effects of hyperbaric treatment on fentanyl release from transdermal fentanyl. The citations are summarized below for your review.

Michniak et al (1996)[2] conducted an in vitro study of the release of fentanyl following hyperbaric treatment with 100% oxygen. Transdermal fentanyl systems (25 mcg/hr) were placed in unoccluded modified Franz diffusion cells at room temperature or 37°C ± 5 °. The transdermal fentanyl system underwent hyperbaric treatment with either 90 minutes of hyperoxia at 2.5 atmospheres or 90 minutes x 3 of hyperoxia every 8 hours. Release profiles were significantly different ($p<0.05$) between temperatures and a trend was noted following the first hyperbaric treatment of an increased release of fentanyl from the patches.

Shirley et al (1997)[3] conducted an in vitro study of the release of fentanyl following hyperbaric treatment with 100% oxygen. Transdermal fentanyl systems (25 mcg/hr) were placed in unoccluded modified Franz diffusion cells at room temperature and release profiles were studied at room temperature, 37, 39, and 42°C and through hairless mouse skin in vitro at 37° C. The transdermal fentanyl system underwent hyperbaric treatment with either 90 minutes of hyperoxia at 2.5 atmospheres or 90 minutes x 3 of hyperoxia every 8 hours. The release from patches receiving hyperbaric treatment were shown to be significantly higher ($p<0.05$) than from untreated patches at 37, 39, and 42°C.

DURAGESIC - Stability - Extreme Heat

BOX WARNING[1]

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®) may be 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 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® 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 generally occur between 20 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 all cytochrome P450 3A4 inhibitors (such as ritonavir, ketoconazole, itraconazole, troleandomycin, clarithromycin, nelfinavir, 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

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 and 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 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. Do not use a DURAGESIC® patch if the 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, heat or tanning 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 exertion should be monitored for opioid side effects and the DURAGESIC® dose should be adjusted if necessary.

PRESCRIBING INFORMATION

Please refer to the following sections of the Full Prescribing Information which are relevant to your inquiry: HOW SUPPLIED

AVAILABLE LITERATURE

A MEDLINE and an internal database literature search (1990 - July 2009) failed to identify any citations relevant to the effects of extreme heat on the stability of the fentanyl transdermal system.

MATRIX FORMULATION

DURAGESIC® was found to be stable for six months at 40° C / 75% relative humidity and 30° C.[4] In cycling studies, DURAGESIC® systems were tested for stability under the following storage conditions:

– cycled from 4° C to 40° C to 4° C over two weeks

– cycled from 25° C to -10° C (freeze-thaw) over 24 hours for three days

In these cycling studies, DURAGESIC® properties, including appearance, were not affected. No significant change in fentanyl content or degradation products was detected. The release profile of the cycled systems was also similar to those stored at room temperature.

RESERVOIR FORMULATION

DURAGESIC® is labeled to store at or below 25° C (77° F). Stability studies (SS1372 and SS1374) indicate that DURAGESIC® systems tested after storage at the following conditions have met product specifications:[4]

– 12 months at 30° C (86° F)

– 1 week at 40° C (104° F) followed by 12 months at 25° C (77° F)

Physical changes begin to occur above 40° C. It is recommended that systems stored beyond the above parameters be discarded.

ENCLOSURE(S):

- DURAGESIC®(fentanyl transdermal system) [package insert]. Raritan, NJ; Ortho-McNeil-Janssen Pharmaceuticals, Inc: July 2009.
- Data on File. Ortho-McNeil Janssen Scientific Affairs, LLC. MSDS-Duragesic Transdermal Systems.

REFERENCE(S):

DURAGESIC® (fentanyl transdermal system)

DURAGESIC - Use with an Occlusive Dressing

1. DURAGESIC®(fentanyl transdermal system) [package insert]. Raritan, NJ; Ortho-McNeil-Janssen Pharmaceuticals, Inc: July 2009.

DURAGESIC - Material Safety Data Sheet (MSDS)

5. Data on File. Ortho-McNeil Janssen Scientific Affairs, LLC. MSDS-Duragesic Transdermal Systems.

DURAGESIC - Effect of Hyperbaric Treatment on Duragesic Release

2. Michniak BB, Piepmeier E, Stroman R, et al. Effects of hyperbaric treatment on fentanyl release profiles from Duragesic® transdermal delivery systems. 10th Anniversary Annual Meeting of the American Association of Pharmaceutical Scientists, Seattle, Washington, USA, October 27-31, 1996. *Pharmaceutical Research* 1996;13(9)(Suppl.):S-379.
3. Shirley DA, Stroman R, Michniak BB, et al. Effect of temperature and hyperbaric treatment on fentanyl release profiles from Duragesic systems, Part II. Annual Meeting of the American Society of Pharmaceutical Scientists, Boston, MA, USA, November 2-6, 1997. *Pharmaceutical Research* 1997. 14(1)(Suppl.):S-318-319.

DURAGESIC - Stability - Extreme Heat

4. Data on File - ALZA Corporation, Mountain View, CA
1. DURAGESIC®(fentanyl transdermal system) [package insert]. Raritan, NJ; Ortho-McNeil-Janssen Pharmaceuticals, Inc: July 2009.