MYLAN LABORATORIES INC.

May 25, 2006

Dockets Management Branch
Food and Drug Administration
Department of Health and Human Services
Room 1061, HFA-305
5630 Fishers Lane
Rockville, MD 20857

DOCKET NO. 2006P-0123: SUPPLEMENT TO CITIZEN PETITION

On March 16, 2006, Mylan Technologies Inc. ("MTI"), a wholly-owned subsidiary of Mylan Laboratories Inc. ("Mylan"), submitted a Citizen Petition ("Petition") under section 505 of the Federal Food, Drug, and Cosmetic Act and 21 C.F.R. § 10.30. The Petition requested that the Commissioner of the Food and Drug Administration (FDA) require all applicants and holders of approved applications for fentanyl transdermal systems to conduct a study to support the safe and appropriate use of an overlay system with their respective patch.

In this Petition Supplement, submitted under 21 C.F.R. § 10.30(g), Mylan provides evidence from its clinical study that demonstrates that an application of a Bioclusive™ overlay system with the Mylan fentanyl transdermal system does not alter the rate and extent of absorption of fentanyl from the patch. In addition, the study concludes that the use of a Bioclusive overlay system is an effective mechanism to ensure continuous contact between the patch and the skin. *See* Attachment A for Summary of Study (A copy of the Study in its entirety is simultaneously being submitted by MTI to the Office of Generic Drugs, Bioequivalence Division, for their review.)

As previously noted in the Petition, continuous contact with the skin is necessary for proper drug delivery from any transdermal product. Disadhesion of a transdermal system may alter the consistent delivery of therapeutic blood levels in patients who use multiple systems throughout the course of therapy. Fentanyl transdermal systems are designed for use in patients with chronic pain and therefore the chances of the use of multiple systems is anticipated. As discussed in the Petition, however, the patches may have a problem "sticking" to the skin. Without continuous contact with the skin, the patient may not get the relief from the severe chronic pain, for which the fentanyl patch is prescribed. This has led patients to use untested devices such as athletic tape to ensure continuous contact with the skin. The innovator/distributor of Duragesic®, Janssen Pharmaceutica Product, L.P., also recognizes "lack of adhesion" as a problem and offers directly to patients upon request, a Bioclusive overlay system to use on top of its patch.

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Although the use of an overlay system can be very effective in making sure that the patch constantly sticks to the skin, an overlay is also sometimes used to enhance penetration of transdermally administered drugs. An opioid analgesic such as fentanyl requires very careful use and monitoring as any increase in penetration or damage to the transdermal system, such as the rupturing of a reservoir containing fentanyl system like Duragesic, can lead to a potentially fatal dose of fentanyl[1]. See Duragesic Labeling section entitled "Safety and Handling".

Accordingly, in the interest of public health and safety, Mylan conducted a clinical study to investigate whether the use of an overlay system with the Mylan fentanyl transdermal system alters the rate and extent of absorption of fentanyl. The overlay system used by Mylan in the conduct of this study was Bioclusive, the same overlay system being made available by Janssen to patients having adhesion problems with Duragesic. The results clearly indicate that the Mylan fentanyl transdermal system with a Bioclusive overlay system is bioequivalent to the Mylan fentanyl transdermal system without a Bioclusive overlay. Moreover, the study indicates that continuous adhesion is maintained with the use of a Bioclusive overlay system. By requiring applicants and holders of approved applications to conduct similar clinical studies, FDA will be assured that use of a specifically identified and tested overlay system with their respective patch does not alter drug delivery and can be used as an intervention to overcome "lack of adhesion".

In addition, with the data generated from a study to support the use of an overlay system, FDA should require all applicants and holders of approved applications to provide information in their respective labeling that identifies which overlay system was tested and, therefore, considered appropriate for use. This will ensure that the public, including, physicians prescribing the product, pharmacists dispensing the product, and patients using the product, have sufficient information to make an informed decision on the appropriate overlay to be used if a patch does not stick to the skin. Examples of the type of language that should be added to the labeling to appropriately inform the public on the correct use of an overlay system for a specific transdermal system is provided in Attachment B.

Sincerely,

John P. O'Donnell
Chief Scientific Officer

[1] The Mylan fentanyl transdermal system does not contain drug in a reservoir. The drug in the Mylan fentanyl transdermal system is within the adhesive, and therefore an application of an overlay system will not cause leakage of fentanyl from the patch.

Attachment A

Summary of Mylan's Study to Assess the Effect of Application of a Bioclusive™ Overlay System with Mylan's Fentanyl Transdermal System

The objective of the clinical study was to investigate the bioequivalence and wearability (adhesion) of the Mylan fentanyl transdermal system as compared to the Mylan fentanyl transdermal system with a Bioclusive overlay system. Forty-one (41) healthy, non-smoking, subjects between the ages of 18 and 61 completed this open-label, two-treatment, two-period, single-dose crossover bioequivalence and wear study[2].

Subjects were housed from the evening prior to dosing until 120 hours after dosing. After a supervised overnight fast (at least 10 hours) each subject received a single 25 μg/h (1 x 25 μg/h) dose of either the Mylan fentanyl transdermal system or the Mylan fentanyl transdermal with a Bioclusive overlay system. Subjects received standard meals during the housing periods. Water was allowed ad lib throughout the study. There were seven (7) days between patch removal and application of the next dose. To minimize the opioid effects of fentanyl, naltrexone hydrochloride 50 mg tablets were administered orally to all subjects at least 12 hours before each patch application and every 12 hours post-application, with the last dose given 72 hours after patch removal. Serial blood samples, 7 mL (1 x 7 mL), were collected at the following times relative to dosing: 0, 2.0, 4.0, 8.0, 12, 18, 24, 32, 40, 48, 56, 64, 72 (before patch removal), 76, 80, 84, 88, 96, 108, 120, and 144 hours. Plasma samples were stored in suitably labeled tubes at -70°C ± 15°C until analysis.

A stringent patch adhesion criteria of greater-than-or-equal-to 90% patch adhesion was required for subjects to be considered valid for assessing the effect of a Bioclusive overlay system. This criteria was specified in the study protocol in order to adequately assess any alterations in pharmacokinetics due solely to application of the overlay.

The method developed for the analysis of fentanyl in human plasma (EDTA) was validated and performed using high performance liquid chromatography with tandem mass spectrometric detection, which had a limit of quantification of 0.0250 ng/mL. The assay demonstrated linearity from 0.0250 ng/mL to 5.00 ng/mL. The interday precision of the assay was less than 10% and interday accuracy was less than 4% of the nominal concentration.

Single-dose pharmacokinetic parameters for fentanyl were calculated using noncompartmental techniques. Statistical analyses were performed on the pharmacokinetic parameters using methodologies standard in the industry for bioequivalence assessment. Single-dose pharmacokinetic parameters, based on the fentanyl plasma concentration-time profiles of the fentanyl transdermal system with and without an overlay system, were found to be comparable with respect to mean values and variability.

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[2] Due to the risk of significant opioid type adverse events (e.g., hypoventilation), the study was conducted with the lowest marketed strength of the Mylan fentanyl transdermal system (25μg/h).

Statistical analysis of the data, comparing the fentanyl transdermal system with an overlay system (Test) to the fentanyl transdermal system without an overlay system (Reference), reveals that 90% confidence intervals for the ratios of Test to Reference are within the acceptable bioequivalent range of 80% and 125% for the natural log transformed parameters LNAUCL (93%-99%), LNAUCI (95%-100%) and LNCPEAK (88%-99%). Accordingly, the study demonstrated that the Mylan fentanyl transdermal system 25 μg/h with a Bioclusive overlay system is bioequivalent to the Mylan fentanyl transdermal system 25 μg/h without a Bioclusive overlay system following a single transdermal 25 μg/h (1 x 25 μg/h) dose worn for three (3) days. Similarly, adhesion of the Mylan fentanyl transdermal system with a Bioclusive overlay system was found to be extremely good. It may be concluded that utilization of a Bioclusive overlay system facilitates a high degree of adhesion to be maintained over 72 hours without affecting delivery of fentanyl from the Mylan fentanyl transdermal system.

Attachment B

PROPOSED LABELING

FENTANYL TRANSDERMAL SYSTEM

Prescribing Information

CURRENT

CLINICAL PHARMACOLOGY: Pharmacokinetics .....

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

The kinetics of fentanyl in geriatric patients have not been well studied, but in geriatric patients the clearance of IV fentanyl may be reduced and the terminal half-life greatly prolonged (see PRECAUTIONS).

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The pharmacokinetics of Mylan's Fentanyl Transdermal System is not altered when a Bioclusive™ Dressing is used as an overlay system to help ensure that adhesion is maintained over 72 hours. A single-dose crossover study in forty-one (41) healthy subjects study demonstrated that the Mylan fentanyl transdermal system 25 μg/h with a Bioclusive overlay system has the same rate and extent of absorption as the Mylan fentanyl transdermal system 25 μg/h without a Bioclusive overlay system following a single transdermal 25 μg/h (1 x 25 μg/h) dose worn for three (3) days.

CURRENT

WARNINGS: .....

Death and other serious medical problems have occurred when people were accidentally exposed to fentanyl transdermal system. Examples of accidental exposure include transfer of a fentanyl transdermal system 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.

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CURRENT

PRECAUTIONS: Information for Patients: A patient instruction sheet is included in the package of fentanyl transdermal systems dispensed to the patient.

Patients receiving fentanyl transdermal system should be given the following instructions by the physician:.....

4. Patients should be advised that fentanyl transdermal system should be applied immediately upon removal from the sealed package and after removal of the protective liner. Additionally the patient should be advised of the following:
   - The fentanyl transdermal system should not be used if the seal is broken, or if it is altered, cut, or damaged in any way prior to application. The transdermal patch 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.
   - The patch should not be folded so that only part of the patch is exposed.

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   - The patch should not be folded so that only part of the patch is exposed.
   - Fentanyl transdermal system may not stick to all patients. If the patch does not stick well or comes loose after applying, Mylan's fentanyl transdermal system may be secured with a Bioclusive™ dressing to help maintain adhesion. If the patch falls off, throw it away and put a new one on at a different skin site.

Patient Information

FENTANYL TRANSDERMAL SYSTEM

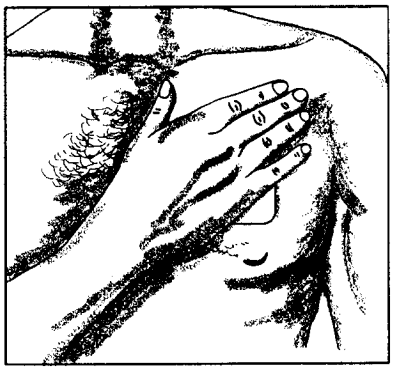
This leaflet contains important information about fentanyl transdermal system. Read this Patient Information carefully before you start using fentanyl transdermal system. Read it each time you get a prescription. There may be new information. This information does not take the place of talking to your health care provider about your medical condition or your treatment. Only your health care provider can decide if fentanyl transdermal system is the right treatment for you. If you do not understand some of this information or have questions, talk with your health care provider.

CURRENT

HOW AND WHERE TO APPLY FENTANYL TRANSDERMAL SYSTEM

In the hospital, your health care provider or other medical person will apply fentanyl transdermal system for you. At home, you or a member of your family may apply fentanyl transdermal system to your skin. You need to check the patches often to make sure that they are sticking well to the skin. In young children and people who have impaired thinking, put the patch on the upper back. This will lower the chances that the patch will be removed.

1. **Prepare:** For adults, put the patch on the chest, back, flank (sides of the waist), or upper.....
3. **Press:** Press the patch onto the skin with the palm of your hand and hold there for a minimum of 30 seconds. Make sure it sticks well, especially at the edges.



- Each fentanyl transdermal system is sealed in its own protective pouch. Do not remove the fentanyl transdermal system from the pouch until you are ready to use it. When you are ready to put on fentanyl transdermal system, tear open the pouch and remove the fentanyl transdermal system.
- Do not put the fentanyl transdermal system on skin that is very oily, burned, broken out, cut, irritated, or damaged in any way.

- If you have any questions about where on your body you should or should not apply the patch, please ask your health care provider.
- Fentanyl transdermal system may not stick to all patients. If the patch does not stick well or comes loose after applying, tape the edges down with first aid tape. If the patch falls off, throw it away and put a new one on at a different skin site (see "DISPOSING OF FENTANYL TRANSDERMAL SYSTEM").
- Wash your hands when you have finished applying fentanyl transdermal system.
- Remove fentanyl transdermal system after wearing it for 3 days (see "DISPOSING OF FENTANYL TRANSDERMAL SYSTEM"). Choose a *different* place on the skin to apply a new fentanyl transdermal system and repeat Steps 1 through 3. Do not apply the new patch to the same place as the last one.

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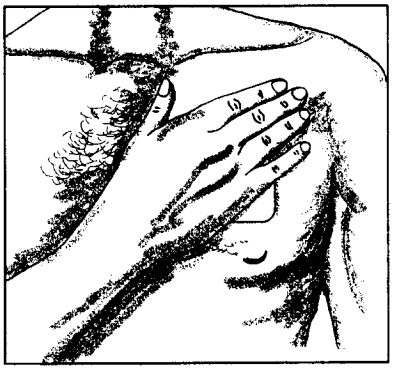

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