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MYLAN LABORATORIES INC.

November 10, 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.

I. FDA Should Require All Holders of Approved Applications for Fentanyl Patch Products and all ANDA Applicants to Include Information in Their Product Labeling Regarding Appropriate Overlays and their Use, and also Require Appropriate Overlays to be Included in All Product Packaging.

Through this supplement, Mylan requests that FDA take further action, first, to require the holder of the reference listed drug, Duragesic®, to amend its labeling to provide instructions for the safe and effective use of overlays. As described in prior submissions on this docket, we understand that an overlay system is provided to consumers of Duragesic upon request, yet no information about the proper use of these overlays appears in the approved labeling for the product. As PriCara (the business unit of Ortho-McNeil Inc. that markets Duragesic) stated in its June 29, 2006 comment to this docket, "[c]urrent labeling for Duragesic, and, by extension, generic formulations of transdermal patches, do not speak to use of an occlusive overlay."

Second, the maker of Duragesic should also be required to include in its product packaging one or more overlays that have been demonstrated through an appropriate bioequivalence trial not to alter the rate and extent of absorption of fentanyl or to increase skin irritation. Including one or more overlays in the product box that is dispensed

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directly to patients is far preferable to distributing overlays only upon receiving a specific adhesion complaint. Not every patient who experiences an adhesion problem would know to contact the maker of the product. No information is included in Duragesic's present labeling that would inform a patient to do this. Unless the patient knew to contact PriCara, the patient would not necessarily receive any information about what types of overlays are or are not appropriate. With a liquid gel filled reservoir product like Duragesic there is an inherent and serious danger of fentanyl gel leakage if the patch is torn or ruptures. A patient who did not appreciate the risks and did not know to contact the product's manufacturer to request an overlay could use an untested and inappropriate adhesive (e.g., duct tape) in an attempt to salvage an expensive, non-adhering patch. In so doing, the patient could possibly rupture or tear a liquid reservoir patch creating a potentially life-threatening situation due to fentanyl gel leakage onto the skin. Even if a patient knew to contact the product's manufacturer, it could take several days for contact to be made and for an overlay to be delivered to the patient. In the interim until the overlay arrives, the patient may have taken inappropriate and potentially dangerous measures to make a non-adhering patch stick. As noted in our prior submissions, patients reportedly have tried anything from athletic tape to waterproof "band aids" in an attempt to make sure that the fentanyl patch continues to stick to the skin. The use of an untested combination of a device with a fentanyl patch poses unknown potential risks.

These same requirements of expanded labeling and including appropriate overlays in the product package should be applied to holders of approved ANDA's and to all pending ANDA applications prior to any further approvals being granted. MTI is prepared to move forward with these measures immediately but cannot presently do so because of the regulatory structure governing generic drug labeling.

As FDA knows, there are presently three approved fentanyl patch products with an AB rating to Duragesic: MTI's Fentanyl Transdermal System, an "authorized generic" version of Duragesic distributed by Sandoz, and a product manufactured by Lavipharm. Under present statutory requirements for ANDA labeling, neither holders of approved ANDA's nor pending generic applicants are permitted to deviate from the approved labeling for the reference listed drug, with few exceptions. See 21 U.S.C. § 355(j)(2)(v). As a result, the makers of generic fentanyl patch products, including MTI, may not include information in their labels about appropriate overlays and their use, nor may overlays be distributed directly in the product packaging, absent corresponding changes having been made first by the holder of the NDA for the reference listed drug, Duragesic.

Mylan therefore requests that FDA require all holders of approved Abbreviated New Drug Applications with an AB rating to Duragesic (including MTI and Lavipharm), and all ANDA applicants seeking approval for an AB-rated fentanyl patch product, to include information in their respective labels about the specific overlays that have been demonstrated through bioequivalence studies to be appropriate and how to use them appropriately. Further, generic applicants and holders of approved ANDA's should be required to include appropriate overlays in their product packages, similar to the requirement we ask FDA to apply to the reference listed drug, Duragesic.

II. Supplemental Information Regarding Use of the Askina® Derm Overlay System with MTI's Fentanyl Transdermal System.

In a Supplement to MTI's Citizen Petition dated May 25, 2006, Mylan provided evidence from its bioequivalence study demonstrating 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, and that the use of a Bioclusive overlay system is an effective mechanism to ensure continuous contact between the patch and the skin.

In its June 29, 2006, comment to this docket noted above, PriCara stated that Alza had conducted a pharmacokinetic trial comparing fentanyl concentrations in subjects using Duragesic with and without an occlusive overlay, but did not disclose the results of that trial at that time. PriCara also explicitly concurred with MTI's request that FDA require all applicants for fentanyl transdermal systems to conduct a study determining the effect of an overlay with their respective patches.

In this Supplement, Mylan is providing information regarding a bioequivalence study on the use of the Askina® Derm overlay system in conjunction with MTI's Fentanyl Transdermal System. The study demonstrates that MTI's Fentanyl Transdermal System 25µg/hr applied without an Askina Derm overlay system is bioequivalent to MTI's Fentanyl Transdermal System 25µg/hr applied with an Askina Derm overlay system, following a single dose worn for three days (72 hours). Continuous skin contact of MTI's Fentanyl Transdermal System was found to be ensured throughout the wear period with the application of the Askina® Derm overlay system. The study further demonstrates that skin irritation is comparable both with and without the Askina Derm overlay system, being minor and quickly resolved in both cases. The study report is being submitted under separate cover to the Agency through controlled correspondence to MTI's approved Abbreviated New Drug Application.

Mylan conducted both bioequivalence studies to investigate whether the use of either of two alternate overlay systems with the MTI Fentanyl Transdermal System alters the rate and extent of absorption of fentanyl or affect levels of skin irritation. The results of both studies clearly indicate that the Mylan FTS used in conjunction with either a Bioclusive™ overlay system or the Askina® Derm overlay system is bioequivalent to the Mylan fentanyl transdermal system without either overlay. Only by requiring all applicants and holders of approved applications to conduct similar bioequivalence studies, can FDA be assured that using a specifically-identified and clinically tested overlay system with their respective patch does not enhance drug delivery and can be used as an intervention to overcome "lack of adhesion."

ENVIRONMENTAL IMPACT

The action requested is subject to a categorical exemption from environmental assessment under 21 C.F.R. §§ 25.22 and 25.31.

ECONOMIC IMPACT

Pursuant to 21 C.F.R. § 10.30(b), MTI will provide data concerning the economic impact of the relief requested should such information be requested by FDA.

CERTIFICATION

The undersigned certifies, that, to the best knowledge and belief of the undersigned, this supplement includes all information and views on which the petition relies, and it includes representative data and information known to the petitioner, which are unfavorable to the petitioner.

Sincerely,



John P. O'Donnell,
Chief Scientific Officer