PriCara
Unit of Ortho-McNeil, Inc.

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Division of Dockets Management
Food and Drug Administration
5630 Fishers Lane, Room 1061 (HFA-305)
Rockville, MD, 20852

Re: Ortho-McNeil concurrence with Mylan's request in their Citizen Petition (2006P-0123 CP1) that the FDA require applicants for fentanyl transdermal systems conduct a study to determine the effect of an overlay with their respective patches

Dear Sir or Madam:

DURAGESIC®, fentanyl transdermal system 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, is manufactured by Alza and has been available in the United States since 1992. It is marketed by PriCara, unit of Ortho-McNeil. In a Citizen Petition, Docket #2006P-0123 CP1, filed with the Dockets Management Branch of the Food and Drug Administration (FDA) on 16 March 2006, Mylan Technologies Inc. (Mylan), a manufacturer of a generic fentanyl transdermal system approved by the FDA in January, 2005, petitioned the Commissioner of the FDA to require all applicants for fentanyl transdermal systems to conduct a study to support the safe use of an overlay with their respective fentanyl transdermal product.

Ortho-McNeil supports this request. Mandating such data will enhance patient safety and reduce the potential for serious adverse consequences should a patient use a product capable of releasing higher rates of fentanyl when an overlay dressing is applied to support adhesion in situations where an occlusive overlay is needed.

This risk for adverse events is greater if a patient is "switched" to a product with potential for enhanced fentanyl release after using a product shown to be safe with the use of an overlay dressing. Mylan correctly notes that "the chances of a patient receiving variable amounts of fentanyl from patch to patch, when intermittently using the same or different overlays, are significantly high because transdermal fentanyl is only prescribed for chronic pain and a patient will most likely use multiple patches throughout the course of therapy. This uncontrollable cycle of different amounts of absorption of fentanyl from patch to patch due to the use of an overlay may unjustifiably increase patient risk." One solution to this dilemma is the insistence by the prescribing physician that the pharmacy dispense a transdermal patch from the same manufacturer (and use of a consistent overlay) with each prescription.

The FDA clearly recognizes the potential for inadvertent delivery of higher-than-anticipated amounts of fentanyl. The FDA Alert for Healthcare Professionals in July 2005 highlighted this concern. The package insert appropriately warns against using patches that are damaged or

cut and to avoid exposing the 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.

In August 2005, to address FDA's concerns over the use of an overlay dressing, the FDA requested that the company conduct a pharmacokinetic trial to compare fentanyl concentrations in subjects using Duragesic with and without an occlusive overlay. Alza, the manufacturer, complied and is analyzing the findings of this trial. In their Citizen Petition, Mylan alluded to "currently undertaking" a study of an overlay with their respective patch.

Ortho-McNeil understands the FDA's concern that use of a fentanyl patch under conditions not studied in clinical trials may lead to serious unanticipated consequences. Current labeling for Duragesic, and, by extension, generic formulations of transdermal patches, do not speak to use of an occlusive overlay. Findings from the Alza pharmacokinetics trial will address concerns relative to the Duragesic patch; if Mylan conducts its study with appropriate rigor, patients using their system may benefit as well. Regardless of the findings, data from these studies cannot be generalized to all fentanyl transdermal patches. Differences in composition that may not impact transdermal delivery of fentanyl under "ideal" conditions in bioequivalence studies may, nonetheless, affect delivery of fentanyl under an occlusive dressing. Such differences in composition include, but are not limited to, fentanyl depot (e.g., reservoir or matrix), use of a rate-limiting membrane (potential for fentanyl crystals to be in direct contact with skin), presence or absence of an enhancer, and quantity of fentanyl in the patch. Furthermore, despite warnings to the contrary, patches that are easily cut, such as those manufactured by Mylan, may present a surface at the cut edge from which fentanyl diffusion may differ under conditions of occlusion.

Accordingly, Ortho-McNeil concurs with Mylan in a call for the FDA to require that applicants for fentanyl transdermal systems conduct a study to determine the effect of an overlay with their respective patches.

Sincerely,

Bruce L. Moskovitz MD

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