DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

FEB 22 2010

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Brian S. Roman
Vice President and General Counsel, North America
Mylan Inc.
781 Chestnut Ridge Road
Morgantown, WV 26505

Re: Docket No. FDA-2009-P-0415

Dear Mr. Roman:

This letter responds to your petition for stay of action (PSA) received on August 27, 2009. In the PSA, you request that the Food and Drug Administration (FDA) stay approval of the application for a "High-Load, Matrix Design Duragesic" or any other fentanyl transdermal product that contains a substantially higher drug load than what is currently on the market (PSA at 1 and 2). You allege that the higher fentanyl content raises a significant public health issue (PSA at 1, 2, and 5). In addition, you also submitted a supplement to the PSA dated January 4, 2010 (Supplement). In the Supplement, you state that even though the PSA was submitted more than 30 days after the date that the Duragesic supplemental new drug application (NDA) was approved, there is good cause for the Commissioner to permit the PSA to be submitted (Supplement at 1). We have carefully considered the PSA and the Supplement. For the reasons stated in this response, the PSA is denied.

I. BACKGROUND

Fentanyl is a potent opioid analgesic and a Schedule II drug. FDA approved the first fentanyl patch, Duragesic, in 1990 (NDA 19-813). Duragesic is manufactured by Alza Corporation and distributed by PriCara, a division of Ortho-McNeil-Janssen Pharmaceuticals, Inc. Sandoz markets an authorized generic of Duragesic. These patches are available in 12.5, 25, 50, 75, and 100 micrograms (mcg)/hour (hr) strengths.

Duragesic is indicated for management of persistent, moderate to severe chronic pain that (1) requires continuous, round-the-clock opioid administration for an extended period of time, and (2) cannot be managed by other means such as nonsteroidal analgesics, opioid combination products, or immediate-release opioids. It is only to 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 25 mcg/hr of fentanyl. The patch provides continuous systemic delivery of fentanyl for 72 hours.

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Duragesic was initially approved as a reservoir patch. In July 2009, FDA approved a supplemental NDA for Duragesic to change its formulation from a reservoir patch to a matrix patch.[1]

FDA has also approved six generic[2] fentanyl patches. Four of the generic fentanyl patches have a matrix design (Mylan Technologies Inc. (ANDA 76-258), Lavipharm Laboratories Inc. (ANDA 77-051), Teva Pharmaceuticals (ANDA 77-449), and Hisamitsu Pharmaceutical Co., Inc. (ANDA 77-775)) and two of the generic fentanyl patches have a reservoir design (Actavis South Atlantic LLC (ANDA 77-062) and Watson Laboratories, Inc. (ANDA 76-709)). All of these patches are available in 25, 50, 75, and 100 mcg/hr strengths. The matrix patch from Mylan Technologies Inc. is also available in the 12.5 mcg/hr strength. Duragesic is the reference listed drug (RLD) for all of these generic fentanyl patches.

II. ANALYSIS

In the PSA, you state that on August 25, 2009, Ortho-McNeil-Janssen Pharmaceuticals, Inc.'s subsidiary PriCara announced that the Duragesic fentanyl transdermal system has a new design (PSA at 1). You allege that the new Duragesic transdermal product has the same indications and dose strengths as the original Duragesic transdermal product but that the gel/liquid filled reservoir design has been replaced with a matrix design that has a substantially higher fentanyl content than the original Duragesic transdermal product and other commercially available fentanyl transdermal systems (PSA at 1).

In the PSA, you request that FDA stay approval of the new Duragesic product or any other fentanyl transdermal product that contains a substantially higher drug content than what is currently on the market (PSA at 1 – 2). You provide a number of claims to support this request, including the following:

1. The substantially higher content of fentanyl in Duragesic presents an increased risk of abuse and diversion of fentanyl, a dangerous and highly addictive drug when used inappropriately (PSA at 1 - 6);

2. The new Duragesic product, which provides the same fentanyl doses over the same period of time (72 hours) for the same indications as currently available fentanyl transdermal products, does not offer any patient benefit over currently available products (PSA at 2 - 3); and

3. Approving a fentanyl patch with a drug load higher than what is on the market would run counter to FDA's heightened efforts to minimize abuse, misuse,

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[1] See description of the Duragesic matrix patch on the Duragesic Web site, available at http://www.duragesic.com/duragesic/duragesic_new_look_info.html.

[2] The term *generic* refers to a drug product for which approval is sought under an abbreviated new drug application (ANDA) submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. 355(j)).

and intentional or unintentional overdose of certain opioid containing products (PSA at 7).

You assert in the PSA that any delay resulting from a stay is not outweighed by the public health or other public interests because other fentanyl transdermal systems are available to address the health needs of the public without posing the same public health danger of abuse and diversion (PSA at 2).

In the Supplement, you state that Mylan learned after submission of the PSA that the supplemental NDA for Duragesic was approved by FDA on July 13, 2009 (Supplement at 1). You assert that even though the PSA was submitted more than 30 days from the date of the approval of Duragesic, there is "good cause" for FDA to permit the PSA to be filed because (1) information regarding the approval of the supplement was not available on FDA's Drugs@FDA database at the time you submitted the PSA, (2) you acted diligently to file the PSA upon learning of the new Duragesic product on August 21, 2009, (3) the timing of Mylan's PSA does not prejudice any other parties, and (4) the PSA raises public health issues.

FDA's regulation at 21 CFR 10.35(b) states, "a request for stay must be submitted...no later than 30 days after the date of the decision involved. The Commissioner may, for good cause, permit a petition to be filed after 30 days." We have reviewed the Supplement and determined that there is good cause to permit the PSA to be filed.

FDA's regulation at 21 CFR 10.35(e) sets out the standard for review of a petition for stay of action as follows:

> The Commissioner may grant or deny a petition, in whole or in part; and may grant such other relief or take such other action as is warranted by the petition. The Commissioner may grant a stay in any proceeding if it is in the public interest and in the interest of justice. The Commissioner shall grant a stay in any proceeding if all of the following apply:
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> (1) The petitioner will otherwise suffer irreparable injury.
> (2) The petitioner's case is not frivolous and is being pursued in good faith.
> (3) The petitioner has demonstrated sound public policy grounds supporting the stay.
> (4) The delay resulting from the stay is not outweighed by public health or other public interests.

In determining whether we shall grant a stay, we need not address whether (1) your request is not frivolous and is being pursued in good faith, (2) you have demonstrated sound public policy grounds supporting the stay, or (3) you have demonstrated that the delay would be outweighed by public health or other public interests because you have not provided any information to demonstrate that you would otherwise suffer irreparable

injury. Therefore, we find that you have not satisfied the first of the four required criteria for a stay.

Although the PSA fails to satisfy the criteria under which FDA *shall* grant a stay, we have discretion to grant a stay under 21 CFR 10.35(e) if it is "in the public interest and in the interest of justice." We have also considered your request for a stay in light of this discretionary standard and decline to exercise our discretion to grant the stay you have requested. Although the Duragesic matrix patch has a higher content of fentanyl than the Duragesic reservoir patch, we have concluded, based on information submitted in the Duragesic application, that this higher amount of fentanyl does not pose an increased risk to patients who use it as indicated in its labeling,[3] and we believe that approval of the Duragesic supplemental application was appropriate under the criteria set forth in section 505(c) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. § 355(c)). We are also unaware of, and you have not provided, any data to show that the Duragesic matrix patch with its higher drug load presents an increased risk of abuse and diversion of fentanyl as compared to fentanyl patches that are currently on the market with a lower drug load. We therefore decline to exercise our discretionary authority under 21 CFR 10.35(e) to grant your request to stay the approval of the Duragesic supplement.

However, we recognize that opioid drugs such as Duragesic have serious risks when used improperly. These risks are clearly articulated in the labeling of opioid drugs, including Duragesic.[4] Despite efforts on the part of FDA, drug manufacturers, and others, the rates of misuse and abuse and of accidental overdose of opioids have risen over the past decade. The Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law 110-85), added section 505-1(a)(2) of the Act (21 U.S.C. 355-1(a)(2)), which authorized FDA to require a risk evaluation and mitigation strategy (REMS) before approving certain applications if FDA determines that a REMS is necessary to ensure that the benefits of a drug outweigh the risks of the drug. Section 505-1 also authorizes FDA to require holders of certain drug applications approved without a REMS to submit a proposed REMS if the Agency becomes aware of new safety information and makes a determination that a REMS is necessary to ensure the benefits of the drug outweigh its risks. Among other things, FDA may consider adverse events occurring from abuse of a drug in requiring a REMS.[5] As you articulated in your PSA (PSA at 7), we are in the process of requiring a REMS for certain opioids, including fentanyl patches, to mitigate the risks associated with the drugs while ensuring that patients with legitimate need for these drugs will continue to have appropriate access (see 74 FR 17967, April 20, 2009).

It is our desire to strike the right balance between two important goals with regard to opioid analgesics: on the one hand, providing access to pain medications for those who

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[3] Product labeling for Duragesic (fentanyl transdermal system), NDA 19-813; Revised July 2009.

[4] Id.

[5] See 21 U.S.C. § 355-1(b).

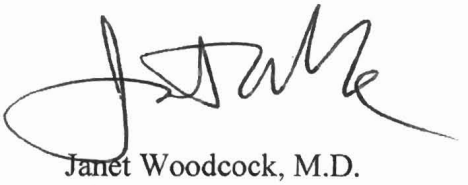
need them, and on the other hand, managing the variety of risks posed by them.[6] Accordingly, although we believe that you have not justified your request that we stay or withdraw approval of the Duragesic patch, we agree that it is prudent to minimize residual drug levels in fentanyl transdermal products and recommend that manufacturers utilize the latest technology to design or redesign their fentanyl patches to achieve this goal. In reviewing new applications for these products, we will continue to apply a science and risk-based approach consistent with the current state of technology to determine whether the residual drug substance in a fentanyl patch at the end of the labeled use period would pose an unreasonable safety risk. We will evaluate any such application and make decisions regarding the application's approvability in the normal course of the application review process.

In addition, we are developing a guidance that will address our current thinking regarding residual amounts of drug in all transdermal products, including fentanyl transdermal products. Upon issuance of a draft guidance, we will provide an opportunity for public comment consistent with our good guidance practices regulation (21 CFR 10.115).

III. CONCLUSION

For the reasons discussed in this response, the PSA is denied.

Sincerely,



Janet Woodcock, M.D.
Director
Center for Drug Evaluation and Research

[6] See Woodcock, J. A difficult balance – Pain management, drug safety, and the FDA. NEJM 361:2105-2107, 2009.