DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

TRANSMITTED BY FACSIMILE

Ajit Shetty, M.D.
CEO
Janssen Pharmaceutica, Inc.
1125 Trenton-Harbourton Road
Titusville, NJ 08560-0200

RE: NDA # 19-813
Duragesic® (fentanyl transdermal system) CII
MACMIS # 12386

WARNING LETTER

Dear Dr. Shetty,

The Division of Drug Marketing, Advertising, and Communications (DDMAC) has reviewed a professional file card (DR-850) for Duragesic® (fentanyl transdermal system) submitted by Janssen Pharmaceutica, Inc. (Janssen) under cover of Form FDA 2253. The file card makes false or misleading claims about the abuse potential and other risks of the drug, and includes unsubstantiated effectiveness claims for Duragesic. The file card thus misbrands the drug under Section 502(a) of the Federal Food, Drug, and Cosmetic Act (Act) 21 U.S.C. 352(a). By suggesting that Duragesic has a lower potential for abuse compared to other opioid products, the file card could encourage the unsafe use of the drug, potentially resulting in serious or life-threatening hypoventilation.

Background

According to the approved product labeling (PI), Duragesic is a transdermal system providing continuous systemic delivery of fentanyl, a potent opioid analgesic, for 72 hours. Duragesic is indicated in the management of chronic pain in patients who require continuous opioid analgesia for pain that cannot be managed by lesser means such as acetaminophen-opioid combinations, non-steroidal analgesics, or PRN dosing with short-acting opioids. The Indications and Usage section of the PI states: "Duragesic should not be used in the management of acute or postoperative pain because serious or life-threatening hypoventilation could result (see BOX WARNING and CONTRAINDICATIONS)." The boxed warning and contraindications sections further discuss the risk of serious or life-threatening hypoventilation. This risk is also addressed in the warnings and precautions sections of the PI.

Duragesic has the potential for abuse. The Drug Abuse and Dependence section of the PI states, in pertinent part:

> Fentanyl is a Schedule II controlled substance and can produce drug dependence similar to that produced by morphine. DURAGESIC® (fentanyl transdermal system) therefore has the

potential for abuse. Tolerance, physical and psychological dependence may develop upon repeated administration of opioids.

False or Misleading Safety Claims

The file card presents the prominent claim, "Low reported rate of mentions in DAWN data," along with Drug Abuse Warning Network (DAWN) data comparing the number of mentions for Fentanyl/combinations (710 mentions) to other listed opioid products, including Hydrocodone/combinations (21,567 mentions), Oxycodone/combinations (18,409 mentions), and Methadone (10,725 mentions). The file card thus suggests that Duragesic is less abused than other opioid drugs.

This is false or misleading for two reasons. First, we are not aware of substantial evidence or substantial clinical experience to support this comparative claim. The DAWN data cannot provide the basis for a valid comparison among these products. As you know, DAWN is not a clinical trial database. Instead, it is a national public health surveillance system that monitors drug-related emergency department visits and deaths. If you have other data demonstrating that Duragesic is less abused, please submit them.

Second, Duragesic is not as widely prescribed as other opioid products. As a result, the relatively lower number of mentions could be attributed to the lower frequency of use, and not to a lower incidence of abuse. The file card fails to disclose this information.

The information from the Drug Abuse and Dependence section of the PI, which appears in a footnote on the opposite page of the spread (entitled "Favorable side-effect profile") is not sufficient to make the claim truthful and non-misleading. The footnote does not substantiate the claim. Nor does it set forth qualifying information about the frequency of prescribing of the compared opioids.

In addition, on the page entitled "Favorable side-effect profile," the file card presents the claim, "Minimizes the potential for local GI side effects by avoiding GI absorption," along with a table entitled, "Adverse experiences in patients with cancer," that shows a 14 percent rate of constipation with Duragesic and a 0 percent discontinuation rate because of constipation. This combination of text and graphics is false or misleading, in that it suggests that Duragesic is associated with less constipation, nausea, and vomiting than oral opioids, which are absorbed by the GI tract. We are not aware of substantial evidence or substantial clinical experience to support this comparative claim.

Unsubstantiated Effectiveness Claims

The file card states, on page four, "Demonstrated effectiveness in chronic back pain with additional patient benefits." The referenced study,[1] conducted by Simpson et al., is inadequate to support this claim, because it was an open-label, single-arm trial with no control group. We are not aware of substantial evidence or substantial clinical experience to support this claim.

On pages 4 and 5, the file card includes the claims, "86% of patients experienced overall benefit in a clinical study based on: pain control, disability in ADLs, quality of sleep," "All patients who experienced overall benefit from DURAGESIC would recommend it to others with chronic low back

[1] Simpson RK Jr, Edmondson EA, Constant CF, Collier C. Transdermal fentanyl as treatment for chronic low back pain. J Pain Symptom Manage. 1997; 14:218-224.

pain," "Significantly reduced nighttime awakenings," and "Significant improvement in disability scores as measured by the Oswestry Disability Questionnaire and Pain Disability Index." To support these claims, the file card again cites the Simpson et al. trial. For the reasons noted above, this uncontrolled study is inadequate to support such claims. We are not aware of substantial evidence or substantial clinical experience to support these claims.

On pages 6 and 7, the file card includes the claims, "Long-term effects: 12-month open-label study," "Significant improvement in physical functioning summary score," and "Significant improvement in social functioning," along with figures illustrating these claims. To support these claims, the file card cites a study[2] conducted by Milligan et al. This open-label, uncontrolled study is not adequate in design to show an analgesic effect. The data from this study are not substantial evidence or substantial clinical experience to support such outcomes claims. We are not aware of substantial evidence or substantial clinical experience to support these claims.

On pages 8 and 9, the file card includes the claims, "Improved patient outcomes: Open-label, crossover comparison study," "Significant improvement in physical functioning summary score," and "Significant improvement in social functioning," along with figures comparing data for Duragesic and sustained release oral morphine. To support these claims, the file card cites the study[3] conducted by Allan et al.. An open-label study cannot minimize bias in the reporting of subjective response in the SF-36, a general healthcare questionnaire. It is therefore not sufficient to support the cited claims. We are not aware of substantial evidence or substantial clinical experience to support these claims.

Finally, the file card prominently presents the claims, "1,360 loaves…and counting," "Work, uninterrupted," "Life, uninterrupted," "Game, uninterrupted," "Chronic pain relief that supports functionality," "Helps patients think less about their pain," and "Improvements in physical and social functioning." These outcome claims are misleading because they imply that patients will experience improved social or physical functioning or improved work productivity when using Duragesic. Janssen has not provided references to support these outcome claims. We are not aware of substantial evidence or substantial clinical experience to support these claims.

Conclusions and Requested Actions

The file card makes false or misleading safety claims and unsubstantiated effectiveness claims for Duragesic. The file card thus misbrands Duragesic in violation of the Act. 21 U.S.C. § 352(a).

DDMAC requests that Janssen immediately cease the dissemination of promotional materials for Duragesic the same as or similar to those described above. Please submit a written response to this letter on or before September 17, 2004, describing your intent to comply with this request, listing all promotional materials for Duragesic the same as or similar to those described above, and explaining your plan for discontinuing use of such materials. Because the violations described above are serious, we request, further, that your submission include a plan of action to disseminate truthful, non-misleading, and complete information to the audience(s) that received the violative promotional materials. Please direct your response to me at the Food and Drug Administration, Division of Drug

[2] Milligan K, Lanteri-Minet M, Borchert K, et al. Evaluation of long-term efficacy and safety of transdermal fentanyl in the treatment of chronic noncancer pain. J Pain. 2001;2:197-204.
[3] Allan L, Hays H, Jensen N-H, et al. Radomised crossover trial of transdermal fentanyl and sustained release oral morphine for treating chronic non-cancer pain. BMJ. 2001;322:1154-1158

Marketing, Advertising, and Communications, HFD-42, Rm. 8B-45, 5600 Fishers Lane, Rockville, MD 20857, facsimile at 301-594-6771. In all future correspondence regarding this matter, please refer to MACMIS # 12386 in addition to the NDA numbers. We remind you that only written communications are considered official.

The violations discussed in this letter do not necessarily constitute an exhaustive list. It is your responsibility to ensure that your promotional materials for Duragesic comply with each applicable requirement of the Act and FDA implementing regulations.

Failure to correct the violations discussed above may result in FDA regulatory action, including seizure or injunction, without further notice.

Sincerely,

{See appended electronic signature page}

Thomas W. Abrams, RPh, MBA
Director
Division of Drug Marketing,
Advertising, and Communications

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Thomas Abrams
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