DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

TRANSMITTED BY FACSIMILE

Roxanne O. McGregor-Beck
Associate Director, Regulatory Advertising and Promotion
Ortho-McNeil-Janssen Pharmaceuticals, Inc.
1125 Trenton-Harbourton Road, Room A207203
Titusville, NJ 08560-0200

RE: NDA # 022304
NUCYNTA® (tapentadol) immediate-release oral tablets C-II
MA # 147

Dear Ms. McGregor-Beck:

This letter notifies Ortho-McNeil-Janssen Pharmaceuticals, Inc. (Ortho-McNeil-Janssen) that as part of its routine monitoring and surveillance program, the Division of Drug Marketing, Advertising, and Communications (DDMAC) of the U.S. Food and Drug Administration (FDA) has become aware of oral statements made by an Ortho-McNeil-Janssen representative on December 8, 2010, at the 2010 American Society of Health-System Pharmacists (ASHP) Midyear Clinical Meeting and Exhibition in Anaheim, CA, regarding its drug NUCYNTA® (tapentadol) immediate-release oral tablets C-II (Nucynta). The representative's statements promote an unapproved use for Nucynta, make unsubstantiated superiority and other claims about the drug, and minimize the serious risks associated with Nucynta. Thus, this promotional activity misbrands Nucynta in violation of the Federal Food, Drug, and Cosmetic Act (Act), 21 U.S.C. 352(f)(1) & (n).

Background

Below is the indication and summary of the most serious and most common risks associated with the use of Nucynta.[1]

According to its FDA-approved product labeling (PI), Nucynta is indicated for the relief of moderate to severe acute pain in patients 18 years of age or older.

Nucynta is associated with serious risks, some of which are potentially fatal. Nucynta is contraindicated in patients with significant respiratory depression, acute or severe bronchial asthma, or hypercapnia in unmonitored settings or the absence of resuscitative equipment. It is also contraindicated in patients with paralytic ileus, in patients taking monoamine oxidase

[1] This information is for background purposes only and does not necessarily represent the risk information that should be included in the promotional activity cited in this letter.

inhibitors (MAOIs), and in patients who have taken MAOIs within the last 14 days. The PI for Nucynta includes warnings and precautions regarding respiratory depression, additive central nervous system (CNS) depression, head injury and increased intracranial pressure, misuse and abuse, impaired mental and/or physical abilities, interactions with alcohol and drugs of abuse, seizures, serotonin syndrome, withdrawal symptoms, hepatic impairment, and use in pancreatic/biliary tract disease.

In addition, according to its PI, 76 percent of Nucynta-treated patients from nine clinical studies experienced adverse events, and the most common adverse reactions in patients treated with Nucynta were nausea, dizziness, vomiting, and somnolence. The PI further states that the most common reasons for discontinuation due to adverse events in Nucynta-treated patients in the studies were dizziness, nausea, vomiting, somnolence, and headache. In the clinical studies, constipation was reported as an adverse event in 8 percent of Nucynta-treated patients versus 3 percent in the placebo arm.

Promotion of Unapproved Use

On Tuesday, December 8, 2010, during the 2010 American Society of Health-System Pharmacists (ASHP) Midyear Clinical Meeting and Exhibition in Anaheim, CA, DDMAC representatives witnessed an Ortho-McNeil-Janssen sales representative indicating that Nucynta is useful in the treatment of Diabetic Peripheral Neuropathic Pain (DPNP).

FDA is not aware of any substantial evidence or substantial clinical experience supporting the use of Nucynta for DPNP. According to its PI, Nucynta is only indicated for the relief of moderate to severe acute pain in patients 18 years of age or older. Although we acknowledge that Nucynta's indication for the relief of moderate to severe acute pain is general, Nucynta is not approved by FDA for the treatment of DPNP, a chronic pain condition that would require a specific indication. In fact, as reflected in the PI, the indication for Nucynta was supported by a 72-hour study, and a 10-day study in patients with moderate to severe acute pain due to bunionectomy surgery and end-stage degenerative joint disease, respectively. The PI does not include any information about the safety or efficacy of Nucynta in the treatment of DPNP. Therefore, the oral statements made by the representative misbrand the drug by creating a new "intended use" for Nucynta for which the PI does not provide adequate directions for use.[2]

Unsubstantiated Superiority Claims/Minimization of Risk

During the December 8, 2010, discussion at ASHP, the Ortho-McNeil-Janssen representative further indicated that:

- DPNP patients stay on Nucynta for longer, and Nucynta provides 10 mg of opioid/oxycodone pain control, similar to tramadol, but with less GI, constipation, nausea, and vomiting.

This claim misleadingly implies that Nucynta is clinically superior (i.e., safer) compared to oxycodone and tramadol for DPNP patients. Specifically, it implies that Nucynta has been shown to have less GI (gastrointestinal) adverse reactions (i.e., constipation, nausea, and

[2] *See* 21 CFR 201.100(c)(1); 21 CFR 201.128.

vomiting), in comparison to oxycodone and/or tramadol, when this is not the case. We note that although safety data was collected from patients taking Nucynta and oxycodone during the clinical studies for Nucynta, FDA determined that the studies were not adequately powered for the analysis of multiple safety endpoints, and that the dose of oxycodone used as a comparator was not demonstrated to be equianalgesic to the doses of Nucynta studied. Therefore, safety comparative data were not considered clinically meaningful and were not included in the approved PI for Nucynta. In addition, FDA is not aware of **any** adequate and well-controlled, head-to-head clinical trials comparing the incidence of constipation, nausea, or vomiting for Nucynta versus tramadol. If you have any evidence to support such claims, please submit it to FDA for review.

Furthermore, the sales representative's claim that Nucynta results in less constipation, nausea, and vomiting minimizes the risks associated with the use of Nucynta and suggests that the drug is safer than has been demonstrated by substantial evidence or substantial clinical experience. As noted in the background section, the most common adverse reactions associated with the use of Nucynta during clinical studies include nausea and vomiting, and these were also among the most common reasons for discontinuation of treatment with Nucynta. Additionally, 8 percent of Nucynta-treated patients experienced constipation as an adverse event in clinical studies versus 3 percent in the placebo arm.

In addition, during the December 8, 2010, discussion at ASHP, the Ortho-McNeil-Janssen representative indicated that when physicians prescribe Nucynta, they:

- won't have to put patients on docusate or senna, patients get out of the hospital a day earlier which saves thousands of dollars because they are going to be able to have a bowel movement.

This claim misleadingly implies that treatment with Nucynta has been shown to reduce length of hospital stay in comparison to oxycodone and tramadol. Specifically, the claim suggests that Nucynta-treated patients will have a bowel movement without the use of docusate or senna, which will result in a reduction in the length of hospital stay compared to oxycodone and tramadol. FDA is not aware of substantial evidence or substantial clinical experience to support such claims. As mentioned above, 8 percent of Nucynta-treated patients reported constipation as an adverse event versus 3 percent in the placebo arm of the clinical studies. In addition, as detailed above, the lack of support for comparing the safety and efficacy of Nucynta to oxycodone and tramadol makes it impossible to make a treatment cost comparison based on the length of hospital stay. If you have any evidence to support such claims, please submit it to FDA for review.

Unsubstantiated Efficacy Claim

The sales representative's statement that Nucynta provides 10 mg of opioid/oxycodone pain control similar to tramadol is misleading because it implies that Nucynta has been shown to be non-inferior to oxycodone, tramadol, or other opioids. Specifically, the claim implies that Nucynta has been shown to provide equivalent "pain control" (equianalgesia) when compared to other opioids, including oxycodone and tramadol. We note that although oxycodone was included as an active comparator arm in the clinical studies for Nucynta, FDA determined that your analyses to obtain a non-inferiority claim regarding the efficacy of Nucynta compared to

oxycodone were inadequate, and the results of those analyses were therefore excluded from the approved PI. In addition, FDA is not aware of any well-controlled head-to-head clinical trials comparing the efficacy of Nucynta to tramadol or any other opioids. If you have any evidence to support this claim, please submit it to FDA for review.

Conclusion and Requested Action

For the reasons discussed above, the oral statements made by the Ortho-McNeil-Janssen representative misbrand Nucynta in violation of the Act, 21 U.S.C. 352(f)(1) & (n).

DDMAC requests that Ortho-McNeil-Janssen immediately cease violative promotional activities for Nucynta such as those described above. Please submit a written response to this letter on or before September 12, 2011, stating whether you intend to comply with this request, listing all promotional materials (with the 2253 submission date) for Nucynta that contain violations such as those described above, and explaining your plan for discontinuing use of such violative materials. Please direct your response to me at the Food and Drug Administration, Center for Drug Evaluation and Research, Division of Drug Marketing, Advertising, and Communications, 5901-B Ammendale Road, Beltsville, MD 20705-1266, facsimile at 301-847-8444. In all future correspondence regarding this matter, please refer to MA# 147 in addition to the NDA number. 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 Nucynta comply with each applicable requirement of the Act and FDA implementing regulations.

Sincerely,

{See appended electronic signature page}

Mathilda Fienkeng, Pharm.D.
Regulatory Review Officer
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/

MATHILDA K FIENKENG
08/26/2011