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E-ALERT | Food & Drug

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SUMMARY OF FDA ADVERTISING AND PROMOTION ENFORCEMENT ACTIVITIES

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This e-alert is part of a monthly series of e-alerts summarizing publicly-available FDA enforcement letters (i.e., warning letters and untitled letters) relating to the advertising and promotion of drugs, biologics, and medical devices. In January 2012, FDA's Office of Prescription Drug Promotion (OPDP) posted the following four enforcement letters on its website:[1]

- Untitled letter to Ortho-McNeil-Janssen Pharmaceuticals, Inc. re: NUCYNTA® (tapentadol) immediate-release oral tablets C-II (August 26, 2011) ("Ortho-McNeil-Janssen Untitled Letter")[2]
- Untitled letter to Mutual Pharmaceutical Company, Inc. re: COLCRYS® (colchicine, USP) tablets for Oral use (December 20, 2011) ("Mutual Untitled Letter")
- Untitled letter to Dr. Reddy's Laboratories, Inc. re: Fondaparinux Sodium Solution for subcutaneous injections (December 22, 2011) ("Dr. Reddy's Untitled Letter")
- Untitled letter to Celgene Corporation re: Abraxane® for Injectable Suspension (paclitaxel protein-bound particles for injectable suspension) (albumin-bound) (December 23, 2011) ("Celgene Untitled Letter")

The Office of Compliance and Biologics Quality (OCBQ) in FDA's Center for Biologics Evaluation and Research (CBER) posted the following enforcement letter on its website:

- Untitled letter to Hospira, Inc. re: Voluven (6% Hydroxyethyl Starch 130/0.4 in 0.9% sodium chloride injection) (December 16, 2011) ("Hospira Untitled Letter")

The Office of Compliance in FDA's Center for Devices and Radiological Health (CDRH) posted the following letter on FDA's website:

- Warning letter to CuraeLase, Inc. re: the CL 1000 IR Laser System (December 9, 2011) ("CuraeLase Warning Letter")

The letters raise a variety of allegations and conclude that the cited advertising/promotional issues render the subject products misbranded and/or adulterated.

This alert merely summarizes the allegations contained in FDA's letters. It does not contain any analysis, opinions, characterizations, or conclusions by or of Covington & Burling LLP. As a result, the information presented herein does not necessarily reflect the views of Covington & Burling LLP or any of its clients.

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[1] Only enforcement letters posted to FDA's website in January 2012 are included herein. Letters issued in January but not posted to the website by January 31, 2012 will be summarized in our alerts for the months in which those letters are posted.

[2] The dates referenced for the letters are the issue dates.

Broadening of Indication

FDA's letters contain the following allegations under a "Broadening of Indication" subheading:

Celgene Untitled Letter: Abraxane is approved for the treatment of breast cancer "after failure of combination chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy. Prior therapy should have included an anthracycline unless clinically contradicted." At the American Society of Clinical Oncology (ASCO) 2010 Annual Meeting, a white paper authored by Abraxis, titled "Nab Technology: A Drug Delivery Platform Utilising Endothelial gp60 Receptor-based Transport and Tumour-derived SPARC for Targeting," suggested that Abraxane is safe and effective in a broader range of conditions and patients than is reflected in the drug's approved product labeling. Specifically, the white paper contained numerous claims relating to the use of Abraxane as a first-line treatment for patients with metastatic breast cancer, and the use of Abraxane in a range of additional cancers for which the drug is under investigation, including head and neck cancer, non small-cell lung cancer, and metastatic melanoma. Further, the white paper failed to disclose the full approved indication for Abraxane, including the indication's limitations.

Promotion of Unapproved Uses[3]

FDA's letters contain the following allegations under a "Promotion of Unapproved Uses" subheading:

CuraeLase Warning Letter: FDA has cleared the CL 1000 IR Laser System with the following indications:

> "The CL1000 IR Laser System is intended to emit energy in the infrared spectrum to provide topical heating for the purpose of elevating tissue temperature for the temporary relief of minor muscle and joint pain and stiffness, minor arthritis pain, or muscle spasm, the temporary increase in local blood circulation and/or promoting relaxation of muscles."

Language on the firm's website and in a promotional brochure claimed that CuraeLase therapy was approved by FDA to treat acute and chronic pain conditions such as fibromyalgia, diabetic neuropathy, plantar fascitis, carpal tunnel, and migraine headaches, among other conditions, and that patients with pain due to diabetic peripheral neuropathy had experienced the return of feeling, reduction of pain, and improved circulation to the extremities after receiving CuraeLase therapy. According to CDRH, the claims appearing on the firm's website and in the promotional brochure represented a "major change in the intended use of the device," rendering the CL 1000 IR Laser System adulterated under section 501(f)(1)(B), and misbranded under section 502(o), of the Federal Food, Drug, and Cosmetic Act (FDCA).

Ortho-McNeil-Janssen Untitled Letter: Nucynta is indicated for the relief of moderate to severe acute pain in patients 18 years of age or older. During the 2010 American Society of Health-System Pharmacists (ASHP) Midyear Clinical Meeting and Exhibition, an Ortho-McNeil-Janssen sales representative stated that the drug is useful in the treatment of Diabetic Peripheral Neuropathic Pain (DPNP). Although FDA acknowledges that Nucynta is indicated for the relief of moderate to severe acute pain generally, OPDP concluded that DPNP is a chronic pain condition that requires a separate indication, which Nucynta does not have. Therefore, the sales representative's statements suggested a new intended use for Nucynta for which it lacks approval.

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[3] The letter issued by CDRH does not explicitly use this subheading, but FDA's allegations fit within this category.

Omission and Minimization of Risk Information

FDA's letters contain the following allegations under an "Omission and Minimization of Risk Information" subheading:

Celgene Untitled Letter: Despite making numerous efficacy claims, the white paper on Abraxane omitted all material risk information from the Boxed Warning, Contraindications, Warnings, and Precautions sections of the approved package insert. The white paper acknowledged several adverse reactions, including hypersensitivity, neuropathy, and neutropenia, but minimized the significance of the overall incidence of neuropathy and neutropenia in patients treated with Abraxane. Additionally, the white paper omitted other adverse reactions and failed to include any warning regarding possible teratogenic effects on a developing fetus. OPDP found that these omissions and minimizations misleadingly suggested that Abraxane was safer than had been demonstrated by substantial evidence or substantial clinical experience.

Dr. Reddy's Untitled Letter: Fondaparinux sodium is indicated for the prophylaxis of deep vein thrombosis in certain patients undergoing surgery. It is also associated with several risks, including epidural and spinal hematomas that could result in long-term or permanent paralysis—risks that are part of the drug's Boxed Warning. OPDP determined that a healthcare professional product information website failed to prominently display the risks associated with fondaparinux sodium and therefore misleadingly suggested that the drug was safer than had been demonstrated by substantial evidence. Specifically, the Boxed Warning describing the risk of epidural or spinal hematomas and paralysis was not presented until the bottom of the webpage, where it was presented as text and as part of a patient video. OPDP concluded that this presentation was unlikely to draw the website viewer's attention. Furthermore, the navigation tab on the left-hand side of the webpage did not include a section on the Boxed Warning, despite listing all other sections of the product label ("PI"). Based on these factors, OPDP concluded that the website undermined the communication of the Boxed Warning and minimized the risks of the drug.

Mutual Untitled Letter: Colcrys tablets are indicated for prophylaxis and the treatment of acute gout flares. Due to the risk of fatal overdoses, blood dyscrasias, life-threatening and fatal drug interactions, and neuromuscular toxicity, Colcrys is contraindicated in patients with renal or hepatic impairment who are receiving P-gp or strong CYP3A4 inhibitors. Additionally, adverse reactions to the drug include diarrhea and pharyngolaryngeal pain. OPDP determined that a pharmacy sell sheet and professional video on Colcrys omitted and minimized the risks of the drug. In particular, the sell sheet included the headline claim "TOUGH BUT GENTLE," (underline added by OPDP) and accompanied the headline with a graphic of a man wearing motorcycle gear holding a china teacup. According to OPDP, this presentation implied that Colcrys is not risky or harmful (i.e., "gentle"), undermining the serious risks associated with the drug. Additionally, the sell sheet included the claim "COLCRYS TOLERABILITY IS COMPARABLE TO PLACEBO," and the professional video claimed that Colcrys had a "tolerability similar to placebo." OPDP found that these claims misleadingly implied that the difference in the safety profiles between Colcrys and placebo was minimal or non-existent. For example, according to the Colcrys' PI, the percentage of patients who experienced diarrhea in clinical trials was 23% in the recommended low-dose group versus 14% in the placebo group. Finally, in OPDP's view, the professional video failed to convey serious and significant risk information associated with Colcrys during the "main part" of the video. Instead, the video presented the majority of the risk information in a running telescript format with accompanying voiceover after the first 15 minutes and 14 seconds of the video. In addition, there was no signal to alert the viewer that important risk information followed the presentation of benefit information.

Overstatement of Efficacy

FDA's letters contain the following allegations under an "Overstatement of Efficacy" subheading:

Mutual Untitled Letter: The professional video on Colcrys misleadingly overstated the efficacy of the drug by implying that the drug effectively reduces pain associated with gout flares within 16 hours. The product labeling for Colcrys provides that the efficacy in the treatment of gout flares was assessed at 24 hours following the time of first dose in the clinical trial. OPDP concluded that this study was not appropriately powered to evaluate outcomes at the 16-hour time point and that neither substantial evidence nor substantial clinical experience demonstrated an effective reduction in pain within 16 hours, contrary to the video's claims.

Unsubstantiated Superiority Claims

FDA's letters contain the following allegations under an "Unsubstantiated Superiority Claims" subheading:

Celgene Untitled Letter: The white paper on Abraxane contained claims that the drug is safer than "conventional" forms of paclitaxel used to treat metastatic breast cancer because Abraxane's formulation contains the naturally-occurring protein albumin and does not contain solvents that may cause serious toxicities. OPDP found that this assertion was not supported by substantial evidence or substantial clinical experience and that the claims minimized the potentially serious risks of Abraxane, such as neutropenia, sensory neuropathy, and possible teratogenic effects on a developing fetus.

Mutual Untitled Letter: The audiovisual presentation in the Colcrys professional video stated that "NSAIDs, which have a black box, are not indicated nor have they ever been approved for the prophylaxis of gout flares. As with all medication, please remember that your gout patients suffer from many comorbid conditions and caution is needed in the concomitant medications you prescribe for your patients." The accompanying screen text on the video stated: "REALITY NSAIDS have never been FDA-approved for gout flare prophylaxis. Many patients with gout have comorbid conditions that preclude the use of NSAIDs long term. COLCRYS is approved for prophylaxis of gout flares as part of the management of gout." OPDP found that the totality of this presentation was misleading for two reasons. First, the video suggested that "there are not significant safety concerns" associated with the use of Colcrys in patients who have comorbid conditions and are taking concomitant medications, when this has not been demonstrated by substantial evidence or substantial clinical experience. Second, it misleadingly implied that Colcrys, when compared to NSAIDs, "is clinically superior (i.e., safer) in patients with comorbid conditions and has fewer drug interactions when taken with concomitant medications compared to NSAIDs[,]" when this has not been demonstrated by adequate and well-controlled head-to-head studies. OPDP's letter notes that these claims were particularly concerning in light of serious warnings in the PI regarding fatal overdoses, blood dyscrasias, life-threatening and fatal drug interactions, and neuromuscular toxicity.

Ortho-McNeil-Janssen Untitled Letter: The Ortho-McNeil-Janssen sales representative stated 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." FDA concluded that this statement misleadingly implied that Nucynta is clinically superior to oxycodone and tramadol for DPNP patients. Additionally, when the sales representative indicated that treatment with Nucynta meant that doctors would not have to put patients on docusate or senna—meaning patients would have bowel movements and be able to leave the hospital earlier—the representative misleadingly implied that treatment with Nucynta has been shown to reduce hospital stay length in

comparison to oxcycodone and tramadol. These claims minimized the risk associated with the use of Nucynta and were not supported by substantial evidence or substantial clinical experience.

Unsubstantiated Efficacy Claims[4]

FDA's letters contain the following allegations under an "Unsubstantiated Efficacy Claims" subheading:

Celgene Untitled Letter: The white paper available at the ASCO Annual Meeting included statements about the "targeted" delivery of Abraxane to tumor cells through "nanoparticle albumin-bound (*nab*™) technology." For example, the paper stated that "[*nab*] technology achieved improved and targeted drug delivery to tumours," and "Abraxane is the first successful example of *nab* technology-based drug-delivery." In OPDP's view, there was no evidence to support these claims, and these statements misleadingly suggested that "'nab technology' and the resulting paclitaxel/albumin formulation of Abraxane actively target the paclitaxel to tumor cells and that this targeted delivery enhances the efficacy and safety of the drug."

Hospira Untitled Letter: Voluven is indicated for the treatment and prophylaxis of hypovolemia. According to OCBQ, a pictorial in the company's sales aid broadened the indication for Voluven by including cardiac pump priming and major abdominal surgery. The Voluven prescribing information indicates that Voluven was studied in patients undergoing various types of surgery, including orthopedic, urologic, and cardiac, but makes no mention of cardiac pump priming or major abdominal surgery as an approved indication for Voluven. Additionally, a statement in the sales aid that Voluven could help avoid edema was misleading because neither substantial evidence nor substantial clinical experience had demonstrated this claim.

Ortho-McNeil-Janssen Untitled Letter: According to OPDP, the company sales representative's statement that Nucynta provided 10 mg of opioid/oxycodone pain control similar to tramadol misleadingly implied that Nucynta has been shown to provide equivalent pain control and was non-inferior to oxycodone, tramadol, or other opioids. As explained above, FDA was unaware of any adequately powered studies comparing the safety and efficacy of Nucynta to oxcyodone or tramadol.

Unsubstantiated Comparative Claims

FDA's letters contain the following allegations under an "Unsubstantiated Comparative Claims" subheading:

Hospira Untitled Letter: Hospira's sales aid for Voluven contained claims that there was a lack of accumulation associated with Voluven compared to hetastarch. Specifically, the sales aid stated that 6% hetastarch was "not easily eliminated and can accumulate in plasma and tissues," but that there was "complete elimination without accumulation" for Voluven. It also stated that Voluven's "distinct molecular properties result in rapid elimination to avoid accumulation." Because these claims were not based on doses cited in Voluven's prescribing information, OCBQ concluded that the sales aid was misleading. Additionally, OCBQ determined that a graph in the sales aid misleadingly indicated that the mean transfusion of packed red blood cells plus whole blood and salvaged blood was lower in patients receiving Voluven than hetastarch, and a statement in the sales aid misleadingly attributed the benefits of sustained plasma volume to the high C_2:C_6 ratio of Voluven. Neither substantial evidence nor substantial clinical experience supported these claims.

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[4] The Hospira Untitled Letter, issued by OCBQ, does not explicitly use this subheading, but the promotional allegations therein fit within this category.

Failure to Provide Adequate Directions for Use

FDA's letters contain the following allegations under a "Failure to Provide Adequate Directions for Use" subheading:

Celgene Untitled Letter: In violation of 21 C.F.R. 201.100(d), the white paper that was available at the ASCO Annual Meeting was not disseminated with the full FDA-approved product labeling for Abraxane.

Failure to Submit Under Form FDA 2253

FDA's letters contain the following allegations under a "Failure to Submit Under Form FDA 2253" subheading:

Celgene Untitled Letter: Abraxis failed to submit a copy of the white paper available at the ASCO Annual Meeting to FDA under cover of Form FDA 2253 at the time of the paper's initial dissemination, in violation of 21 C.F.R. 314.81(b)(3)(i).

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If you have any questions concerning the material discussed in this client alert, please contact the following members of our food & drug practice group:

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