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E-ALERT | Food & Drug

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SUMMARY OF FDA ADVERTISING AND PROMOTION ENFORCEMENT ACTIVITIES

NOVEMBER 2013

This e-alert is part of a series of monthly e-alerts summarizing publicly-available FDA enforcement letters (i.e., warning letters and untitled letters) relating to the advertising and promotion of prescription drugs, medical devices, and biologics.

In November 2013, FDA's Office of Prescription Drug Promotion (OPDP) posted the following enforcement letters on FDA's website[1]:

- Warning letter to Aegerion Pharmaceuticals, Inc., re: NDA 203858 JUXTAPID™ (lomitapide) capsules, for oral use MA #31 (November 8, 2013) ("Aegerion Warning Letter")
- Warning letter to Kadmon Pharmaceuticals, LLC, re: Ribasphere® RibaPak® (ribavirin, USP) tablets MA #72 (November 18, 2013) ("Kardmon Warning Letter")
- Untitled letter to Daiichi Sankyo, Inc. re: NDA #021286 & 021532 BENICAR® (olmesartan medoxomil) tablets, for oral use, BENICAR HCT® (olmesartan medoxomil – hydrochlorothiazide) tablets MA #527 (November 5, 2013) ("Daiichi Untitled Letter")
- Untitled letter to US WorldMeds, LLC, re: Revonto® (dantrolene sodium) for injection MA #44 (November 8, 2013) ("WorldMeds Warning Letter")
- Untitled letter to Duchesnay, Inc. re: NDA #021876 DICLEGIS (doxylamine succinate and pyridoxine hypochloride) delayed-release tablets, for oral use MA #3 (November 12, 2013) ("Duchesnay Untitled Letter")
- Untitled letter to Amgen, Inc. re: BLA #103951 Aranesp® (darbepoetin alfa) MA #920 (November 19, 2013) ("Amgen Untitled Letter")

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

- Warning letter to Mectra Labs Inc. re: Electro-Lube; Magnified Insufflation Needle; A Light Insufflation Endoscopic Needle (November 14, 2013) ("Mectra Warning Letter")
- Warning letter to Shoney Scientific India re: Disposable Biopsy Punches and other devices (November 20, 2013) ("Shoney Warning Letter")
- Warning letter to Blueshine/Hyperion Medical re: HyperBlue 1530/Blueshine Gold Series (November 20, 2013) ("Hyperion Medical Warning Letter")

[1] Only enforcement letters posted to FDA's website in November 2013 are included herein. Letters issued in November but not posted to the website by November 30, 2013 will be summarized in our alerts for the months in which those letters are posted.

The Office of Compliance and Biologics Quality (OCBQ) in FDA's Center for Biologics Evaluation and Research (CBER) did not post any enforcement letters relating to advertising and promotion on FDA's website.

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.

LETTERS ISSUED BY OFFICE OF PRESCRIPTION DRUG PROMOTION (OPDP)

Aegerion Warning Letter

Juxtapid is indicated as an adjunct therapy to reduce certain types of cholesterol in patients with homozygous familial hypercholesterolemia ("HoFH"). The product label includes a Boxed Warning regarding the risk of hepatotoxicity, and the drug is available through a restricted program under a Risk Evaluation and Mitigation Strategy ("REMS"). OPDP alleged that statements made by the Chief Executive Officer ("CEO") of Aegerion Pharmaceuticals, Inc. on two episodes of CNBC's "Fast Money" television show provided "evidence that Juxtapid is intended for new uses, for which it lacks approval and for which its labeling does not provide adequate directions for use. . . ."

Lack of Adequate Directions for Use: OPDP alleged that the following statements by the CEO were misleading:

- "In these [HoFH] patients, they have a devastating disease. . . they're born with this disease and often not diagnosed until 8, 10, years of age when they have a heart attack. . .[a]nd then they have another event, usually about every 18 months, and die by the age of 30. And we've found out that we can lower it significantly with this drug. . . ."
- "And the drug is corrective against that disease and that's the most important thing. If you think about some oncology products that may lengthen life three months or six months, this product has the potential of taking a patient that would die at 30 and allow them to meet their grandkids."
- "These patients are going to die of a cardiac event, either a stroke or a heart attack, if we don't have them on therapy."

According to OPDP, these statements suggested that Juxtapid decreases heart attacks and strokes and increases the lifespan of patients with HoFH. The product label, however, specifically includes a limitation of use stating that the effect of the drug on cardiovascular morbidity and mortality has not been determined. OPDP also alleged that the statements implied that Juxtapid is safe and effective as a monotherapy, which is not an approved use. Finally, OPDP claimed that the statements were presented without any mention of risks associated with the drug. OPDP requested that Aegerion submit a comprehensive plan to address its concerns, including corrective messaging about the intended use of Juxtapid.

Kadmon Warning Letter

Ribasphere, in combination with peginterferon alfa-2a, is indicated for the treatment of adults with chronic Hepatitis C virus infection who have compensated liver disease and have not been previously treated with interferon alpha. The approved product label has Boxed Warnings regarding the lack of efficacy of Ribasphere monotherapy, the risk of hemolytic anemia, and other risks. OPDP contended

that a promotional letter regarding Ribasphere omitted important risk information, broadened the approved patient population, omitted material facts, and made unsubstantiated efficacy claims.

Omission of Risk Information: OPDP alleged that the letter failed to include any risk information. Although the letter referred readers to safety information provided with the letter, OPDP claimed that "the inclusion of a separate document with the safety information [did] not mitigate the misleading representations within the body of the letter."

Broadening of Patient Population or Condition: The letter stated that "**Ribasphere . . . may help improve patient adherence to [Hepatitis C Virus ("HCV")] medication, leading to improved rates of [Sustained Virologic Response ("RSV")]**.[2] According to OPDP, this claim was misleading because it implied that Ribasphere is approved as a monotherapy to treat all patients with Hepatitis C. In fact, Ribasphere has been approved only as a combination therapy and only in those adults with chronic Hepatitis C virus infection who have compensated liver disease and have not been previously treated with interferon alpha. OPDP noted that the inclusion of the statement in the body of the letter that "[f]inishing a weekly pack serves as a reminder to administer the peginterferon injection" did not correct the allegedly misleading impression that Ribasphere can be used as a monotherapy.

Omission of Material Fact: OPDP alleged that the letter omitted material information from the INDICATIONS AND USAGE section of the product label concerning points to consider when initiating Ribasphere treatment. Specifically, OPDP contended that the letter failed to explain that the indication is based on clinical trials of limited duration, with restricted patient populations and results.

Unsubstantiated Efficacy Claims: The letter included the following claims:

> "As an expert in the treatment of Hepatitis C, you understand first-hand the complexity of chronic HCV treatment. Patients with HCV require extensive education about how to take their medication and the importance of taking all medication as prescribed. In addition, the significant pill burden and side effects of HCV therapy can quickly lead to non-adherence.
>
> **Ribasphere . . . may help improve patient adherence to HCV medication, leading to improved rates of SVR.**
>
> - The only 2 pill/day ribavirin at all doses. . .
> - Unique compliance pack. . . .Pills are clearly labeled for 7 days of AM and PM dosing. . . ."[3]

According to OPDP, the above claims misleadingly suggested that a medication regiment with Ribasphere will have a positive impact on patient adherence, as well as HCV treatment overall. Although the letter included citations to literature, OPDP alleged that the references did not describe adequate and well-controlled studies assessing adherence endpoints or clinical outcomes that specifically examined Ribasphere. Further, though OPDP acknowledged that some of the claims were factually correct (e.g., "Pills are clearly labeled for 7 days of AM and PM dosing"), OPDP stated the overall impression of the letter was misleading. OPDP requested that Kadmon provide a plan for corrective action, including submitting corrective messages to the audiences that received the letter.

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[2] Emphasis in letter.
[3] Emphasis in letter and citations omitted.

Daiichi Untitled Letter

OPDP alleged that a professional direct mailer regarding Benicar and Benicar HCT was misleading because it made unsubstantiated efficacy claims.

Unsubstantiated Efficacy Claims: The direct mailer included the following claims and presentations:

- "Which hypertensive therapy helped 7 out of 10 challenging patients reach goal?"
- "In the BeniSYS trial, 70% of patients reached a BP goal of <140/90 mm Hg by week 12 (mean baseline BP: 171/95 mm Hg)."[4]
- A bar graph depicting the following changes in mean SBP (mm HG) from baseline: minus 17 for Benicar 20 mg, minus 18 for Benicar 40 mg, minus 30 for Benicar HCT 40/12.5 mg, and minus 35 for Benicar 40/25 mg.[5]
- "26 patients (15.4%) achieved BP normalization of <120/80 mm Hg and exited the study and last observation was carried forward; these patients are included in the 70% who reached goal."[6]

OPDP contended that the above claims were misleading because they implied that Benicar and Benicar HCT can help reduce high blood pressure in "challenging patients" without adequate substantiation. OPDP stated that references cited in support of the claims described the results of an open-label, uncontrolled trial, which lacked placebo control or blinding, and thus did not support the claims in OPDP's view. OPDP further alleged that the referenced study excluded some "challenging patients" such as those with severe hypertension. Finally, OPDP stated that the bar graph depicted a reduction in blood pressure that was greater than that seen in Benicar's pivotal trials.

WorldMeds Untitled Letter

OPDP alleged that a webpage entitled "About Revonto" was misleading because it presented unsubstantiated superiority claims and omitted and minimized important risk information.

Unsubstantiated Superiority Claims: The webpage included the following claims:

- "**Revonto** offers a significant advancement in patient pharmacotherapy with its improved ease of reconstitution. This feature allows operating room teams to be better equipped to manage an [malignant hyperthermia ("MH")] crisis."[7]
- "**Revonto** puts time on your side. . . ."[8]

OPDP alleged that the above claims implied that Revento's improved ease of reconstitution represented a significant advancement in patient pharmacotherapy that correlates with an improvement in overall MH crisis management compared to other MH treatments. OPDP stated that there are no references supporting these alleged superiority claims, which should be supported by head-to-head clinical trials.

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[4] Citation omitted.
[5] Citations omitted.
[6] Citation omitted.
[7] Emphasis in webpage.
[8] Emphasis in webpage.

Omission/Minimization of Risk Information: According to OPDP, the webpage presented various efficacy claims but omitted risk information from the WARNINGS and PRECAUTIONS sections of the product label. OPDP stated that there were links to the Full Prescribing Information on the webpage, but this did not mitigate the misleading impression. OPDP also stated that the webpage minimized risk information because it displayed efficacy claims in large, bold, and colorful font and graphics, but in contrast, displayed risk information below the site map on the bottom of the page and in single-spaced paragraph format.

Duchesnay Untitled Letter

Diclegis is indicated for the treatment of nausea and vomiting of pregnancy in women who do not respond to conservative management. According to OPDP, a form letter to healthcare providers from the company announcing the approval of Diclegis was misleading in that it failed to communicate any risk information associated with its use and omitted material facts.[9]

Omission of Risk Information: OPDP alleged that the following statements in the letter constituted efficacy claims:

- "Today I am pleased to inform you that the U.S. Food and Drug Administration has approved Diclegis indicated for the treatment of nausea and vomiting of pregnancy (NVP) in women who do not respond to conservative management."
- "Millions of pregnant women could benefit from an approved NVP treatment and Diclegis represents a much needed FDA-approved treatment option."

OPDP stated that the alleged claims above must be accompanied by risk information, which was not provided in the letter.

Omission of Material Fact: OPDP claimed that the letter failed to state a material limitation regarding the use of Diclegis. Although OPDP acknowledged that the letter provided Diclegs' indication, OPDP contended that the letter was misleading because it failed to convey that Diclegis has not been studied in women with hyperemesis gravidarum. This limitation is included under the "Limitations of Use" heading of the Indications and Usage section of the approved label.

Amgen Untitled Letter

OPDP alleged that a direct mailer regarding Aranesp was misleading because it omitted risk information, suggested Aranesp is useful in a broader patient population or condition, made unsubstantiated efficacy claims, and omitted material facts.

Omission of Risk Information: OPDP acknowledged that the direct mailer included a presentation of Aranesp's Boxed Warning and other risk information. OPDP alleged, however, that it failed to include other material facts under subheadings of the WARNINGS and PRECAUTIONS section of the product label. OPDP stated that references to the full prescribing information and the Aranesp website did not mitigate the omission of risk information from the direct mailer.

Broadening of Patient Population or Condition: The direct mailer presented the following claims:

[9] OPDP also alleged that Duchesnay did not comply with 21 CFR 201.10(g)(1) because the letter failed to present the established name of the drug in conjunction with the proprietary name, nor 21 CFR 201.100(d) because the letter was not disseminated with the full FDA-approved product labeling.

- "For chemotherapy-induced anemia (CIA) in metastatic patients with [Hemoglobin ("Hb")] <10 g/dL."
- "Catch hemoglobin levels before they fall too far," presented in conjunction with an image of a man, composed of red blood cells, in a free-fall.

According to OPDP, these claims suggested that Aranesp is useful to treat chemotherapy-induced anemia in any patient with metastatic cancer whose hemoglobin is falling or has fallen below 10g/dL. OPDP claimed that this was misleading because the approved indication includes limitations such as "treatment of anemia in patients with non-myeloid malignancies where anemia is due to the effect of concomitant myelosuppressive chemotherapy." OPDP acknowledged that the approved indication was included on page three of the direct mailer; however, OPDP alleged that this information did not mitigate the impression that Aranesp is useful in a broader range of patients.

Unsubstantiated Efficacy Claims: Page three of the direct mailer included the headline, "Reduce RBC transfusions and achieve a **gradual and steady** Hb rise with Aranesp."[10] According to OPDP, the statement that a "gradual and steady" Hb rise with treatment was inconsistent with the product label's recommendation that dosage be reduced if hemoglobin levels increase greater than 1 g/dL in any 2-week period. OPDP also stated that the pivotal studies cited to support the claim that Hb rise was "gradual and steady" did not include the rate of Hb rise as endpoints.

Page three of the direct mailer also stated that "[i]n untreated patients whose Hb fell below 10 g/dL, 1 in 3 required an [Red Blood Cell, ("RBC")] transfusion within 6 weeks" and that "Aranesp significantly reduced the need for RBC transfusions by 48% compared to placebo." OPDP alleged that the presentation suggested that Aranesp reduces the need for RBC transfusion from 1 in 3 to approximately 1 in 6, when the CLINICAL STUDIES section of the product label states 1 in 4 Aranesp-treated patients require an RBC transfusion. OPDP also contended that the claim that 1 in 3 untreated patients required an RBC transfusion was unsubstantiated because the references cited to support the claim described post-hoc, exploratory, and pooled analyses of placebo-treated patients from six different clinical trials.

Omission of Material Fact: The direct mailer stated that "Aranesp can be synchronized with the majority of chemotherapy regiments, including [every three week treatment, ("Q3W")]." According to OPDP, the mailer should have included additional information regarding the approved dosing of Aranesp with this claim (which OPDP stated involves "extensive instructions" regarding dosing schedules, monitoring requirements, and dose adjustments).

[10] Emphasis added by OPDP.

LETTERS ISSUED BY OFFICE OF COMPLIANCE (OC) IN CDRH[11]

Mectra Warning Letter

OC alleged that three devices, the Magnified Insufflation Needle ("MAGI"), A Lighted Insufflation Endoscopic Needle ("ALIEN"), and Electro-Lube were adulterated and misbranded because they were being marketed outside cleared specifications on Mectra Labs' website.

The website stated that the MAGI and ALIEN needles were "[a]vailable in 75 mm, 120 mm and 150 mm." OC contended that the cleared devices contained needles of 120 mm and 150 mm only, and that a 75 mm needle constituted a modification requiring clearance under Section 510(k). In addition, according to OC, the devices as marketed used LED lights to indicate the placement of the needle within the peritoneal cavity, instead of an indicator band on the needle as in the cleared devices. OC alleged that this change also raised questions of safety and effectiveness and constituted a modification requiring a new premarket submission. OC stated that the new indicator includes "additional elements in the signal transition chain" and thus poses a risk of providing the wrong signal to the user.

According to OC, the website also indicated that promotional claims for the Electro-Lube established intended uses for the device that were beyond its cleared uses. OC stated that Electro-Lube was cleared as a single patient use device intended to be used on electrodes to reduce sticking, but the website included claims for specific clinical applications such as general surgery, gynecology, and "HUNDREDS of OTHER applications." OC alleged that these were new indications, which constituted a major change or modification requiring a new premarket notification or application.

Shoney Warning Letter

OC contended that, among other manufacturing-related violations, Shoney Scientific India failed to seek marketing clearance or approval for its Disposable Biopsy Punch. OC alleged that though such devices may be exempt from premarket notification under 21 C.F.R. § 872.4565 and 21 C.F.R. § 872.9(a), Shoney Scientific India's website provided evidence that the Disposable Biopsy Punch had a different intended use than the exempted devices. OC noted that 21 C.F.R. § 872.4565 defines exempt devices of this type as "hand-held device[s] intended to perform various tasks in general dentistry and oral surgery procedures." However, OC alleged that the website claimed that the Disposable Biopsy Punch could be used for clinical applications such as "correcting vitiligo" and "hair transplant." OC alleged that those claims established an intended use that exceeded the scope of the exemption in 21 C.F.R. § 872.4565, and thus the company had to submit a premarket notification or application for these intended uses.

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[11] In addition to the letters issued by OC, the Office of In Vitro Diagnostics and Radiological Health ("OIR") issued a Warning Letter to 23andMe that was extensively covered in the media. According to OIR, 23andMe marketed a Saliva Collection Kit and Personal Genome Service ("PGS") as a medical device without premarket clearance or approval. OIR stated that the website included the following claims regarding PGS:

- PGS provides "health reports on 254 diseases and conditions, including categories such carrier status, health risks, and drug response;" and
- PGS is a "first step in prevention that enables users to take steps toward mitigating serious diseases such as diabetes, coronary heart disease, and breast cancer."

According to OIR, these statements indicate that PGS is marketed as a Class III device in part because its intended uses may allegedly "lead a patient to undergo prophylactic surgery," "carry the risks that patients relying on such tests may begin to self-manage their treatments," and increase the "risk of serious injury or death [from self-management or incorrect results]."

Hyperion Medical Warning Letter

OC alleged that the Blueshine Gold Series diode laser was cleared for wavelengths of 980 nm but Hyperion Medical's website claimed that the device can also use 940 nm, 808 nm, and 532 nm wavelengths as single wavelengths or in combination with other wavelengths. Further, OC stated that, according to the website, a 15 mm hand piece (which was not cleared by the agency in the 510(k)) was added to the HyperBlue 1530 diode laser device. OC contended that these changes raised safety and effectiveness questions and constituted modifications requiring new premarket submissions under Section 510(k).

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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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