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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 alert is part of a monthly series of 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 2010, FDA's Division of Drug Marketing, Advertising, and Communications (DDMAC) posted the following seven enforcement letters (all untitled) on its website:[1]

- Treanda® (bendamustine hydrochloride) for Injection, Cephalon, Inc. (Dec. 18, 2009)[2]
- Byetta® (exenatide) injection, Amylin Pharmaceuticals, Inc. (Dec. 24, 2009)
- Mirena® (levonorgestrel-releasing intrauterine system), Bayer Healthcare Inc. (Dec. 30, 2009)[3]
- Cymbalta (duloxetine hydrochloride), Eli Lilly and Company (Jan. 7, 2010)
- Visipaque™ (iodixanol) injection, GE HealthCare (Jan. 7, 2010)
- Isovue® (iopamidol injection), Bracco Diagnostics Inc. (Jan. 7, 2010)
- Dysport (abobotulinumtoxinA) for Injection, Baumann Cosmetic & Research Inst. (Jan. 11, 2010)

The letters address the following issues: Omission/Minimization of Risk Information; False/Misleading Statements; Overstatement of Efficacy; Broadening of Indication/Promotion of Unapproved Use; Omission of Material Fact; Promotion of an Unapproved Drug; Unsubstantiated Comparative Claims; and Failure to Submit Form FDA 2253. Except as otherwise noted, DDMAC's letters conclude that the cited advertising/promotional issues render the subject product misbranded and/or an unapproved new drug.

This alert merely summarizes the allegations contained in DDMAC'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 during January 2010 are included herein. Letters issued in January but not posted to the website by January 31, 2010 will be summarized in our alerts for the months in which those letters are posted. As of the date of publication of this alert, the following additional letters, issued in January, have been posted on the DDMAC website: OraVerse (phentolamine mesylate) Injection, Novalar Pharmaceuticals, Inc. (issued Jan. 22, 2010, posted Feb. 2, 2010); BenzaClin® (clindamycin 1% - benzoyl peroxide 5%) gel, sanofi-aventis U.S. LLC (issued Jan. 22, 2010, posted Feb. 2, 2010); ASTELIN® (azelastine hydrochloride) Nasal Spray, Meda Pharmaceuticals, Inc. (issued Jan. 26, 2010, posted Feb. 2, 2010); and Adcirca™ (tadalafil) Tablets, Lilly Corporate Center (issued Jan. 27, 2010; posted Feb. 2, 2010).

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

[3] The Treanda, Byetta, and Mirena letters were issued in December 2009, but were not posted on the DDMAC website until January 12, 2010. DDMAC did not issue any warning letters in January 2010. Neither the Advertising and Promotional Labeling Branch (APLB) in FDA's Center for Biologics Evaluation and Research nor the Center for Devices and Radiological Health (CDRH) posted any applicable letters on its website in January.

OMISSION/MINIMIZATION OF RISK INFORMATION

DDMAC untitled letter to Cephalon, Inc. (Dec. 18, 2009) ("Cephalon untitled letter"): A pocket dosing card for Treanda® (bendamustine hydrochloride) for Injection included an "extremely limited" risk presentation on the back cover under the header, "Important Safety Information." The presentation omitted "critical" details about the risks disclosed, including the fact that certain risks are "frequent, severe and potentially **fatal**." (emphasis added by DDMAC).

DDMAC untitled letter to Bayer HealthCare Pharmaceuticals, Inc. (Dec. 30, 2009) ("Bayer untitled letter"): A script for a live consumer-directed program for Mirena® (levonorgestrel-releasing intrauterine system) omitted from its risk presentation contraindications regarding untreated lower genital tract infections and conditions associated with increased susceptibility to pelvic infections. The presentation also did not adequately convey that should a woman become pregnant while using Mirena, she may lose her baby or become infertile. Additionally, the script minimized the risks associated with Mirena by including a statement about women "looking and feeling great" while using the product even though the package insert (PI) includes "very common" adverse reactions (experienced by >10% of clinical trial patients), in addition to other serious warnings, precautions, and safety issues associated with the use of the product.

DDMAC untitled letter to Bracco Diagnostics, Inc. (Jan. 7, 2010) ("Bracco untitled letter"): A website for Isovue® (iopamidol injection) omitted the drug's boxed warning regarding intrathecal administration, as well as other important risk information, such as "the potential for serious, life-threatening, fatal anaphylactoid or cardiovascular reactions." Statements such as, "Please click on the 'downloads and PI' tab for full prescribing information" were insufficient to mitigate the misleading omission of risk information. Moreover, certain webpages failed to present risk information with comparable prominence to the presentations about the safety advantages of Isovue. Specifically, the letter notes differences between font sizes and the placement of graphics on the website, and the fact that risk information was "relegated to the end of the video in a telescript format, with rapidly scrolling small text in single-spaced paragraph format, and with a voiceover that [was] spoken in a noticeably faster pace than in the efficacy presentations."

DDMAC untitled letter to Eli Lilly and Company (Jan. 7, 2010) ("Eli Lilly untitled letter"): A direct-to-consumer print advertisement for Cymbalta (duloxetine hydrochloride) failed to communicate any risk information in the main part of the ad. The main body of the ad included a prominent graphic along with various efficacy claims in large, bolded, and colorful text and graphics. This portion of the ad, however, "entirely omit[ted]" risk information, including the contraindications, warnings and precautions, as well as the most frequently reported adverse reactions from the package insert (PI). Although the ad contained the statement, "**See left page for Important Safety Information, including Boxed Warning**" (emphasis in original) at the bottom of the page and contained risk information on an adjacent page, this was insufficient to mitigate the overall misleading presentation. Further, the accompanying risk information was placed in a single column in a single-spaced paragraph on a page with unrelated advertisements and magazine content.

A WebMD Little Blue Book Rheumatology edition with a fibromyalgia message for Cymbalta (duloxetine hydrochloride) failed to present risk information with a prominence and readability reasonably comparable to the efficacy presentation. For instance, one spread contained an efficacy claim in a "very large bolded yellow font on a blue background with significant white space." In contrast, the risk information was presented on the preceding pages in a smaller black font and in single-spaced paragraph format. In addition, the "Important Safety Information" header appeared two pages before the efficacy claim (in the reverse order in which this information is typically presented), making it not visible to viewers looking at the efficacy spread. The presentation on the

back cover of the message also minimized the risks associated with Cymbalta. The back cover contained a product image, as well as efficacy information, but no risk information. Risk information was presented inside the back cover and on the preceding page. However, a package insert (PI) booklet was affixed to the inside back cover, thereby obscuring the immediately preceding page of risk information. Additionally, the title of the PI, "Prescribing Drug Information for The WebMD Little Blue Book 2008 Edition RH-CYM," gave no clear information as to the content of the PI or the risk information beneath the PI booklet. Finally, the statement, "**See Important Safety Information, including Boxed Warning, on previous pages. Please see accompanying booklet for full Prescribing Information**" (emphasis in original) – which appeared in small type at the bottom of pages containing efficacy claims – did not mitigate the misleading minimization of risk information.

DDMAC untitled letter to GE Healthcare (Jan. 7, 2010) ("GE Healthcare untitled letter"): A website for Visipaque™ (iodixanol) injection omitted important information from the drug's bolded warning pertaining to inadvertent intrathecal administration, along with other important risk information, such as "the potential for serious, life-threatening, fatal anaphylactoid or cardiovascular reactions." A link to the Visipaque PI on the left-hand side of the website was insufficient to mitigate the misleading omission of risk information. Explicit and implicit claims that the product has an "excellent safety profile" further minimized the risks associated with Visipaque, especially in light of the fact that the product has a boxed warning, bolded warning, and numerous contraindications, warnings, precautions, and adverse events associated with its use. Finally, unlike the sections marked with bolded headers such as, "Product Highlights" and "Product Description," the risk information on the website had no such signal and was placed at the very bottom of the webpage after the reference list.

OVERSTATEMENT OF EFFICACY

DDMAC untitled letter to Amylin Pharmaceuticals, Inc. (Dec. 24, 2009) ("Amylin untitled letter"): Oral statements regarding Byetta® (exenatide) injection made by a Lilly representative at the Endocrine Society's Annual Meeting misleadingly overstated the efficacy of the product. Specifically, the Lilly representative stated that Byetta has a positive effect on cholesterol and triglyceride levels and that because of this effect, "cardiovascular benefits" are associated with product use. FDA is not aware of any substantial evidence or substantial clinical experience to support this claim.

Bayer untitled letter: A script for a live consumer-directed program for Mirena® (levonorgestrel-releasing intrauterine system) contained unsubstantiated claims that overstated product efficacy. Certain statements indicated that the use of Mirena instead of other means of contraception would result in increased levels of intimacy, romance, and, by implication, emotional satisfaction. FDA is not aware of any evidence to support this implication. According to the Mirena package insert (PI), "at least 5% of clinical trial patients reported **decreased libido** as a side effect of Mirena use," along with abdominal/pelvic pain, nausea, headache, nervousness, and depressed mood, all of which could adversely affect a woman's feelings relating to romance or intimacy. (emphasis added by DDMAC). Additionally, the script contained claims suggesting that Mirena could help patients "look and feel great." FDA is not aware of any evidence to support this outcome either. According to the PI, patients using Mirena may experience various side effects, such as irregular bleeding, ovarian cysts, back pain, weight increase, breast pain/tenderness, and acne.

Eli Lilly untitled letter: A WebMD Little Blue Book Rheumatology edition with a fibromyalgia message for Cymbalta (duloxetine hydrochloride) contained a claim that 53% of fibromyalgia patients treated with Cymbalta had a 30% improvement in pain severity. The claim cited "data-on-file," and these data consisted of a pooled analysis of the results from two Cymbalta clinical studies presented in the package insert (PI). Unlike the data in the PI, however, these data were reanalyzed using a last-

observation-carried-forward (LOCF) imputation method. DDMAC states that an analysis of the clinical study data using an LOCF imputation method does not constitute substantial evidence or substantial clinical experience to support promotional claims. Since 40 to 60% of the dropouts in these clinical studies were due to adverse events, carrying forward a good score (i.e., relying on LOCF) for patients who dropped out was misleading, since dropping out for lack of efficacy or for toxicity was itself a negative outcome.

FALSE/MISLEADING STATEMENTS

Amylin untitled letter: Oral statements regarding Byetta® (exenatide) injection made by a Lilly representative and an Amylin representative at the Endocrine Society's Annual Meeting exaggerated the weight loss demonstrated in clinical trials with Byetta. When a DDMAC representative queried the Amylin representative about the data in support of the weight loss claim, the DDMAC representative was escorted to Amylin's Medical Information booth and provided with two reprints. Neither of these reprints provides substantial evidence to support the weight loss claims made by the representatives; rather, they contain some data from the clinical trials in Byetta's PI, which do not reflect the weight loss results described by the representatives.

Bayer untitled letter: A script for a live consumer-directed program for Mirena® (levonorgestrel-releasing intrauterine system) included a claim that Mirena had "**no** daily, weekly, or **monthly routines to comply with** as compared to the negatives associated with other birth control methods." (emphasis added by DDMAC). This claim "directly contradicts" information contained in Mirena's package insert (PI), such as the direction that patients be reexamined and evaluated "4 to 12 weeks after insertion and once a year thereafter, or more frequently if clinically indicated." The PRECAUTIONS, Patient Counseling Information section also states that patients should check that the threads attached to Mirena are in place after each menstrual cycle (thus on a monthly basis) to ensure that Mirena has not become displaced or expelled. Although the script included instructions to check the threads monthly in a separate part of the presentation, this did not correct the appearance of the false statement elsewhere in the script.

Bracco untitled letter: A website for Isovue® (iopamidol injection) contained numerous false claims and presentations regarding the design of the IMPACT study. For instance, in various places, the website indicated that IMPACT was a prospective study that compared the endpoint of incidence of contrast-induced nephropathy (CIN) between Isovue (iopamidol-370) and Visipaque (iodixanol-320). The IMPACT study was not such a study, but rather was a post-hoc combination of two already-completed trials, INVICTA and VIRPACT, that were designed to study image quality as a primary endpoint and that listed CIN risk as a secondary endpoint. DDMAC notes that in addition to falsely characterizing the design of the IMPACT study, the website presented comparative claims based on IMPACT suggesting that Isovue is in fact numerically superior to Visipaque in its impact on CIN rate and provides the "best possible image and greatest level of safety" compared to Visipaque. The IMPACT study, however, does not constitute substantial evidence or substantial clinical experience to support such comparative claims. DDMAC also specifically notes that an implied claim about Isovue's superior image quality and safety "greatly minimize[d] the serious risks associated with the drug" and the IMPACT study was not designed to evaluate imaging quality as an endpoint.

BROADENING OF INDICATION/PROMOTION OF UNAPPROVED USE

Amylin untitled letter: Oral statements regarding Byetta® (exenatide) injection made by a Lilly representative at the Endocrine Society's Annual Meeting broadened the product's indication. The Lilly representative made the following claim in word or substance to a DDMAC representative: "Although Byetta is not indicated for use by itself because it was not FDA approved this way and the

FDA requires additional studies, Byetta can be used by itself." Although FDA subsequently approved Byetta for a monotherapy indication, the version of the package insert (PI) approved for Byetta at the time the representative made these statements "clearly stated that the product was indicated as **adjunctive** therapy to improve glycemic control." (emphasis added by DDMAC). The caveat given by the representative that Byetta was not indicated for use by itself did not mitigate the overall impression created by the presentation that Byetta is effective for, and should be used as, monotherapy. DDMAC further notes that the representative made these statement five months prior to Byetta's approval for the monotherapy use and, therefore, they also constituted promotion of the product for an unapproved use.

OMISSION OF MATERIAL FACT

Cephalon untitled letter: A pocket dosing card for Treanda® (bendamustine hydrochloride) for Injection omitted "important material information" related to the dosing claims on the front of the card. Specifically, it failed to communicate the potential need for dose delays, modifications, reinitiation, and discontinuation of therapy for both hematologic and non-hematologic toxicities of Treanda. Inclusion of the statement, "Please see accompanying full Prescribing Information for dose modifications, interruptions, or discontinuation," on the bottom left corner of the front cover was insufficient to correct the misleading omission of material dosing information from the card itself.

PROMOTION OF AN UNAPPROVED DRUG

DDMAC untitled letter to Dr. Leslie Baumann (Jan. 11, 2010): Statements made by a clinical investigator in a magazine and during a television program pertaining to the drug abobotulinumtoxinA for Injection (referred to as "Dysport" – the U.S.-approved trade name) violated FDA's Investigational New Drug regulations because they suggested that Dysport was safe and effective before it was approved, and also that it was superior to an approved product, Botox. DDMAC notes that the suggestion of superiority, in addition to constituting the promotion of the product before approval, was misleading in that it is not supported by substantial evidence or substantial clinical experience. DDMAC notes the existence of mechanisms by which clinical investigators and sponsors may engage in the full exchange of scientific information concerning drugs that are under investigation, but states that the promotional activities in which this clinical investigator engaged did not constitute such exchange.

UNSUBSTANTIATED COMPARATIVE CLAIMS

GE Healthcare untitled letter: A website for Visipaque™ (iodixanol) injection contained claims suggesting that Visipaque offers a safety benefit compared to other products due to its unique formulation and that it is safer than other contrast media in high risk patients. FDA is not aware of substantial evidence or substantial clinical experience to support this implication. DDMAC notes that based on data in the package insert (PI), "Visipaque was only **comparable** in efficacy and safety to other ionic and nonionic imaging agents studied." (emphasis added by DDMAC). The reference provided to support the claim that Visipaque offers a greater safety benefit than similar products for high risk patients states only that angiographic and procedural complications "**tended** to be less frequent" for the Visipaque group compared with the other contrast agent group. (emphasis added by DDMAC). Additionally, the website included unsubstantiated claims suggesting that Visipaque offers excellent images and results in better diagnostic outcomes compared to other products. The references cited in support of these claims do not support this implication, and furthermore the PI states only that results with Visipaque were "**similar** to those of the active controls." (emphasis added by DDMAC).

FAILURE TO SUBMIT FORM FDA-2253

GE Healthcare untitled letter: A website for Visipaque™ (iodixanol) injection violated 21 C.F.R. § 314.81(b)(3)(i) because the manufacturer did not submit a copy of the website to FDA under cover of Form FDA-2253 prior to initial dissemination.

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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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