In November 2008, FDA’s Division of Drug Marketing, Advertising, and Communications (DDMAC) posted two warning letters and one untitled letter on its website. The letters addressed the issues below. This summary describes only DDMAC’s allegations. It does not reflect the recipient’s response or analysis by Covington & Burling.

**Omission/Minimization of Risk**

Two professional direct mailers for Cedax® (ceftibuten capsules and ceftibuten for oral suspension) were misleading because they presented numerous efficacy claims for Cedax but failed to reveal material risk information associated with use of the drug. For example, the direct mailers included the following efficacy claims: “Convenient once-a-day dosing . . .”; “High penetration into the middle ear fluid and bronchial secretions”; and “Enhanced stability against beta-lactamase-producing pathogens.” Despite these claims, the only risk disclosure presented for Cedax was the following statement: “Low incidence of diarrhea (only 4% in children).” The mailers failed to present any of the other risks reflected in the package insert (PI), including the bolded warning regarding serious hypersensitivity reactions. Furthermore, the statement regarding the low incidence of diarrhea was framed as a positive claim and was presented under a bullet titled “Excellent tolerability” along with another positive claim about the drug. The totality of these omissions and representations created the misleading impression that Cedax is safer than has been demonstrated by substantial evidence or substantial clinical experience. (Shionogi USA, Inc., November 14, 2008)

A flash card for Tracleer® (bosentan) tablets presented numerous efficacy claims, but it failed to communicate some of the most serious and important risks associated with the use of Tracleer. The use of Tracleer is contraindicated in patients treated concomittantly with cyclosporine A due to markedly increased plasma concentrations of bosentan. The use of Tracleer is also contraindicated in patients treated concomittantly with glyburide due to an increased risk of liver enzyme elevations. Despite the seriousness of these risks, the flash card failed to include either contraindication. The fact that the flash card contained the statement “Please see accompanying full prescribing information” (emphasis in original) did not mitigate these misleading omissions. (Actelion Pharmaceuticals US, Inc., November 24, 2008)

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1 The Advertising and Promotional Labeling Branch (APLB) in FDA’s Center for Biologics Evaluation and Research (CBER) did not issue any letters in November.
Unsubstantiated Superiority Claims

A flash card for Tracleer® (bosentan) tablets presented a table of various claims regarding the superiority of Tracleer therapy versus sildenafil therapy. Specifically, the table, which was presented in conjunction with the claim, “When initiating PAH therapy . . . Don’t take NO for an answer” (emphasis in original), included the following questions: “Indicated to reduce the risk of clinical worsening?”; “Over 2 years of follow-up data in [pulmonary arterial hypertension (PAH)] clinical trials?”; “Prescribed to over 40,000 PAH patients, and over 5 years of clinical PAH experience?”; and “Blocks the devastating effects of endothelin?” The answers presented in response to each of these questions were “YES” for Tracleer and “NO” for sildenafil (emphasis in original). The overall presentation suggested that Tracleer is a better treatment option than sildenafil when physicians are initiating PAH therapy for a patient. Although the answers in the flash card presentation may have been true, without a comparison of the risks associated with the products, the flash card misleadingly suggested that Tracleer is a better treatment option for PAH than sildenafil. In addition, the flash card omitted material information about other attributes of Tracleer therapy, including serious risks, that are highly relevant to any decision about whether to prescribe Tracleer or sildenafil. Tracleer is associated with serious and significant risks that are not a concern when using sildenafil in PAH patients. For example, Tracleer is approved under a risk management program including restricted distribution (the TRACLEER® Access Program) and is associated with a boxed warning due to the risks of potential liver injury and major birth defects. Sildenafil, however, has none of these restrictions or warnings. This comparative presentation in the flash card misleadingly omitted any mention of these attributes of the drugs and therefore suggested that Tracleer is a superior therapy. (Actelion Pharmaceuticals US, Inc., November 24, 2008)

Broadening of Indication/Failure to State Full Indication

Two professional direct mailers for Cedax® (ceftibuten capsules and ceftibuten for oral suspension) were misleading because they suggested that Cedax is effective in a broader range of conditions than has been demonstrated by substantial evidence or substantial clinical experience. Specifically, the direct mailers included claims suggesting efficacy of the drug as an anti-infective, such as “High penetration into the middle ear fluid and bronchial secretions” and “Enhanced stability against beta-lactamase-producing pathogens.” But the direct mailers failed to present the full indication for the product, including the specific infections for which the drug is indicated and the limitation that Cedax is approved only for the treatment of mild-to-moderate infections. The direct mailers therefore misleadingly implied that Cedax is effective for the treatment of any middle-ear or bronchial infection. They also failed to reveal that Cedax is approved for use only against susceptible strains of designated microorganisms and to identify the list of organisms for each indication, thus suggesting that Cedax is effective against a wider range of pathogens than has been demonstrated. Other important material limitations to pathogen coverage and the use of Cedax were also misleadingly omitted from the pieces, contributing to the impression that the drug is useful in a broader range of conditions than has been demonstrated by substantial evidence or substantial clinical experience. (Shionogi USA, Inc., November 14, 2008)

Misleading Claims

Two professional direct mailers for Cedax® (ceftibuten capsules and ceftibuten for oral suspension) claimed that Cedax is associated with “[h]igh penetration into the middle ear fluid and bronchial secretions” but failed to include any context to clarify the meaning of “high” penetration. With regard to middle ear fluid and bronchial penetration, the Cedax package insert (PI) states that mean concentrations of ceftibuten in epithelial lining fluid...
and bronchial mucosa in adults were only 15% and 37%, respectively, of the plasma concentrations, and that ceftibuten middle-ear fluid area under the curve (AUC) in pediatric patients averaged approximately 70% of the plasma AUC. Without information about the actual level of penetration, this claim of high penetration was misleading because it overstated the efficacy of the product. (Shionogi USA, Inc., November 14, 2008)

Promotion of an Investigational New Product

A webpage titled “Voraxaze™—an enzyme that breaks down methotrexate (MTX)” and a product fact sheet titled “Voraxaze™ for methotrexate toxicity” for investigational new drug Voraxaze™ (glucarpidase) contained claims that either promoted the safety or efficacy of Voraxaze or otherwise promoted the drug for the reduction of methotrexate levels in patients who are experiencing, or at risk for, methotrexate toxicity due to impaired or delayed methotrexate elimination. For example, the webpage and fact sheet presented the following claims: “Voraxaze™ . . . is a biological product designed to rapidly reduce the amount of blood levels of methotrexate (MTX), a commonly used cancer drug in the blood,” and “Voraxaze™ is the only drug which can remove MTX from the blood; dialysis is the only other way to remove MTX from the blood.” In addition to promoting Voraxaze for the reduction of methotrexate levels in patients who are experiencing or are at risk for methotrexate toxicity, some of the claims in the pieces promoted that Voraxaze may be effective for “routine” or “planned” use with high-dose methotrexate to optimize the high-dose methotrexate therapy. In combination with the other claims about the safety and efficacy of Voraxaze, the webpage and product fact sheet strongly suggested that the drug would be safe and effective for this use as well. These claims were misleading because neither the webpage nor the product fact sheet revealed that there are no data to support the efficacy of the drug for this use or that the risks for routine, planned use are unknown. This omission is particularly problematic from a public health perspective because routine administration of Voraxaze could have serious safety and efficacy implications. Specifically, Voraxaze is a protein that is foreign to the body, and the risk of an allergic reaction and/or anaphylaxis may increase following repeat doses. Voraxaze may also become ineffective after repeated doses (i.e., with routine use) due to the presence of neutralizing antibodies. (Protherics Inc., November 14, 2008)

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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:

This information is not intended as legal advice, which may often turn on specific facts. Readers should seek specific legal advice before acting with regard to the subjects mentioned herein.

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