Food & Drug

E-ALERT November 18, 2008

SUMMARY OF DDMAC AND APLB ENFORCEMENT CORRESPONDENCE

October 2008

In October 2008, FDA's Division of Drug Marketing, Advertising, and Communications (DDMAC) posted two warning letters and one untitled letter on its website, and the Advertising and Promotional Labeling Branch (APLB) in FDA's Center for Biologics Evaluation and Research (CBER) posted one untitled letter on its website.[1] The letters addressed the issues below. This summary describes only DDMAC's and APLB's allegations. It does not reflect the recipient's response or analysis by Covington & Burling.

Omission/Minimization of Risk

A consumer-directed pharmacy printout for Mirapex® (pramipexole dihydrochloride) presented numerous efficacy claims for Mirapex, including "Restless Legs Syndrome (RLS) is a real condition, with real day-to-day consequences" and "If you said YES to these questions [in a patient quiz], you may have a treatable condition called Restless Legs Syndrome (RLS)." But the printout failed to present any risk information about Mirapex. A second printout discussed common side effects associated with Mirapex and stated, "Side effects are mild and decreased over time. The most common side effects are nausea, headache and tiredness." This presentation, however, failed to communicate that serious warnings are associated with Mirapex. Specifically, the printout failed to include the warnings about falling asleep during activities of daily living, symptomatic hypotension, and hallucinations. By omitting these risks, the printout misleadingly suggested that Mirapex is safer than has been demonstrated. Stating that "[s]ide effects are mild and decreased over time" also minimized the risks associated with the drug and reinforced the message that Mirapex is safer than has been demonstrated. The statement "Please see accompanying Patient Information for MIRAPEX" included on the bottom third of the printouts did not mitigate these misleading presentations. (Boehringer-Ingelheim, September 29, 2008) (DDMAC)

Two direct-to-consumer (DTC) broadcast television advertisements for YAZ® (drospirenone and ethinyl estradiol) tablets minimized the serious risks associated with YAZ through the use of distracting visuals, numerous scene changes, and other competing modalities, such as the background music. For example, in one advertisement, the fast-paced visuals depicted various women looking at pictures, trying on clothes, chatting at a cafe, stretching/exercising in a park, and walking down the street, while the audio component described the major risks associated with YAZ. These complex presentations distracted from and made it difficult for viewers to process and comprehend the important risks being conveyed. This presentation was particularly troubling because some of the risks conveyed are serious and even life-threatening. (Bayer HealthCare Pharmaceuticals, Inc., October 3, 2008) (DDMAC)

[1] The Mirapex letter was issued on September 29, 2008, but was not posted until October 2. The Thrombate III letter was issued on September 5, 2008, but was not posted until October 10.

A direct-to-consumer (DTC) patient brochure for Sensipar® (cinacalcet HCl) tablets was misleading because it omitted and minimized risks associated with Sensipar treatment, thus implying that Sensipar is safer than has been demonstrated by substantial evidence or substantial clinical experience. Specifically, the brochure entirely omitted some of the serious risks associated with Sensipar, including the risk of adynamic bone disease, and it failed to disclose the risk of Sensipar therapy to patients with hepatic impairment. Additionally, the brochure made the following claims under the headline "Are there side effects?": "Sensipar® is well tolerated. The most common side effects are nausea, vomiting, and diarrhea. Sensipar® side effects typically last a short time." The headline "Are there side effects?" in this presentation implied that the subsequent text contained a comprehensive list of the drug's side effects, but the text instead presented only the most common adverse events associated with Sensipar therapy. Furthermore, the brochure presented the following claim within the "Important Safety Information" section on the back cover of the brochure: "While on Sensipar®, your doctor may have to do blood tests." This presentation minimized the need for continual laboratory monitoring of serum calcium, serum phosphorous, and intact parathyroid hormone (iPTH) levels associated with Sensipar. According to the package insert (PI), these levels should be monitored at regular intervals during Sensipar therapy, but the brochure misleadingly suggested that monitoring may not be necessary for some patients, thereby minimizing the risk of hypocalcemia associated with the drug. Finally, the brochure failed to present the serious risk information with a prominence and readability reasonably comparable with the presentation of information relating to the effectiveness of the drug. It prominently presented efficacy claims throughout several pages of the brochure with colorful graphics, ample white space, and descriptive headers, whereas it presented the warnings and precautions in a single paragraph on the back cover of the brochure. Inclusion of the statement, "*Please see accompanying Sensipar® package insert for full product information*" (emphasis in original) on the back cover of the brochure and a removable PI in the interior pocket of the brochure did not mitigate the misleading omission and minimization of risk information in the brochure itself. (Amgen, October 27, 2008) (DDMAC)

Misleading and Unsubstantiated Superiority and Comparative Claims

A sell sheet for Thrombate III® (Antithrombin III, Human) included a table comparing Thrombate III and fresh frozen plasma (FFP). The headings for the table read: "Thrombate III . . . the Necessary Therapy" and "Fresh frozen plasma (FFP) is contraindicated for a coagulopathy when the missing protein is available as a concentrate." The table also compared Thrombate III and FFP with respect to efficacy, dosing, "safety processing," adverse events, side effects, storage, and "convenience." The overall presentation of the table misleadingly suggested that Thrombate III is safer and more effective than FFP when none of these characteristics has been compared in an adequately and well-controlled manner. (Talecris Biotherapies, Inc., September 5, 2008) (APLB)

Misleading Safety Claims

A sell sheet for Thrombate III® (Antithrombin III, Human) was misleading because it suggested that Thrombate III is safer than has been determined by substantial evidence or substantial clinical experience. Specifically it stated that that "Thrombate III reduces the risk of thrombotic events without increasing the risk of bleeding." But use of Thrombate III for hemostasis is associated with significant safety risks, particularly involving the interaction of Thrombate III and heparin. The Warnings section of the Thombate III package insert (PI) states that the anticoagulant effect of heparin is enhanced by concurrent treatment with Thrombate III in patients with hereditary antithrombin III (AT) deficiency. Thus, in order to avoid bleeding, reduced dosage of heparin is recommended during treatment with Thrombate III. The statement regarding the risk of bleeding was therefore misleading. (Talecris Biotherapies, Inc., September 5, 2008) (APLB)

Overstatement of Efficacy

A direct-to-consumer (DTC) broadcast television advertisement for YAZ® (drospirenone and ethinyl estradiol) tablets was misleading because it suggested that YAZ is more effective than has been demonstrated by substantial evidence or substantial clinical experience. For example, the advertisement's theme song "Good-Bye to You" played in the background of the advertisement as energetic, euphoric, playful women released into the air balloons displaying words representing certain symptoms associated with premenstrual dysphoric disorder (PMDD) (e.g., irritability, moodiness, feeling anxious, bloating, fatigue, muscle aches, headaches, increased appetite, and acne). The balloons then floated up and away from the women, misleadingly suggesting that the women were saying "goodbye" to their PMDD symptoms, despite the fact that neither substantial evidence nor substantial clinical experience has demonstrated that treatment with YAZ eliminates these symptoms. Similarly, the advertisement, as well as a second DTC advertisement for YAZ, included close-up images of women with completely clear, acne-free skin, along with audio claims that YAZ helps keep skin clear. The data in the package insert (PI), however, do not demonstrate that YAZ results in clear, acne-free skin for a typical woman; rather, these data demonstrate only that YAZ reduces the amount of acne lesions more than placebo. Thus the advertisements misleadingly overstated the efficacy of the drug. (Bayer HealthCare Pharmaceuticals, Inc., October 3, 2008) (DDMAC)

Broadening of Indication/Failure to State Full Indication

Two direct-to-consumer (DTC) broadcast television advertisements for YAZ® (drospirenone and ethinyl estradiol) tablets misleadingly suggested that YAZ is effective in a broader range of patients and conditions than has been demonstrated by substantial evidence or substantial clinical experience. For example, one of the advertisements stated, "We all know that birth control pills are 99% effective and can give you shorter, lighter periods. But did you know there's a Pill that could do more?" It then displayed images of energetic, euphoric, playful women singing "We're Not Gonna Take It" as they kicked, punched, and pushed words representing symptoms such as "IRRITABILITY," "MOODINESS," "BLOATING," and "FEELING ANXIOUS" away from the screen, followed by the claim "It's YAZ! And there's no other birth control like it." The screen then displayed another list of symptoms including irritability, increased appetite, moodiness, fatigue, feeling anxious, headaches, bloating, and muscle aches. These symptoms are commonly seen in women with premenstrual syndrome (PMS), for which YAZ is not approved. Conversely, premenstrual dysphoric disorder (PMDD), for which YAZ is approved, is a disorder whose hallmarks include markedly depressed mood, anxiety or tension, affective lability, persistent anger or irritability, as well as decreased interest in usual activities, difficulty concentrating, lack of energy, change in appetite or sleep, and feeling out of control. The advertisements entirely omitted the material limitation from the package insert (PI) for YAZ, namely that YAZ has not been evaluated for the treatment of PMS, and they failed to convey that the drug is indicated only for women who have PMDD rather than PMS. In addition, the advertisements misleadingly suggested that YAZ is approved for the treatment of acne of all severities. Specifically, in one advertisement, the word "ACNE" appeared in large print in the middle of the screen along with the audio claim "It can also help keep your skin clear," which was accompanied by a close-up visual of a woman with completely clear skin. These presentations failed to adequately convey that, as noted in the PI, "YAZ is indicated for the treatment of moderate acne vulgaris" (emphasis added). (Bayer HealthCare Pharmaceuticals, Inc., October 3, 2008) (DDMAC)

A direct-to-consumer (DTC) patient brochure for Sensipar® (cinacalcet HCl) tablets stated, "**For patients on dialysis** Help your lab values **move in the right direction with Sensipar®**" (emphasis in original). This presentation was false or misleading because it failed to communicate the drug's full approved indication, including material limitations, and thereby broadened the indication of Sensipar. Specifically, Sensipar is not indicated for all patients on dialysis but is indicated only for chronic kidney disease patients on dialysis who require treatment for secondary hyperparathyroidism. Inclusion

of the full indication on the back cover of the patient brochure was insufficient to mitigate the misleading impression created by the initial presentation that Sensipar is useful in a broader range of conditions or patients than has been demonstrated by substantial evidence or substantial clinical experience. (Amgen, October 27, 2008) (DDMAC)

Omission of Material Fact

A professionally directed labeling piece for Mirapex® (pramipexole dihydrochloride) included claims and representations about restless leg syndrome (RLS) and Mirapex but failed to present the corresponding approved indication for Mirapex (i.e., that Mirapex is indicated for the treatment of moderate-to-severe primary RLS). One side of the piece presented numerous claims regarding RLS but did not mention the name of the product. The reverse side included a section titled "IMPORTANT SAFETY INFORMATION ABOUT MIRAPEX." The piece thus tied use of Mirapex to treatment of RLS but failed to include the drug's full indication for use. Additionally, the claims presented in the piece regarding RLS misleadingly implied that Mirapex is useful in a broader range of conditions or patients than has been demonstrated by substantial evidence. For example, the piece presented claims such as "Which of these patients suffers from RLS? They all do!" and "RLS affects a range of patients." In the absence of disclosure of Mirapex's approved indication, these claims were misleading in the context of the overall presentation because they suggested that Mirapex is safe and effective for use in the treatment of RLS regardless of severity, when in fact Mirapex is approved for use only in the treatment of moderate to severe RLS. (Boehringer-Ingelheim, September 29, 2008) (DDMAC)

Failure to Provide Adequate Directions for Use

Two consumer-directed pharmacy printouts for Mirapex® (pramipexole dihydrochloride) were distributed without the Mirapex package insert (PI) as required by 21 C.F.R. § 201.100(d). (Boehringer-Ingelheim, September 29, 2008) (DDMAC)

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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