Food & Drug

E-ALERT

February 17, 2009

SUMMARY OF DDMAC AND APLB ENFORCEMENT CORRESPONDENCE

January 2009

In January 2009, FDA's Division of Drug Marketing, Advertising, and Communications (DDMAC) posted two untitled letters on its website.[1] 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

A Continuum Care Pharmacy formulary flashcard for Depakote® (divalproex sodium delayed-release) Tablets and Depakote® ER (divalproex sodium extended-release) Tablets was misleading because it presented numerous efficacy claims for Depakote and Depakote ER but failed to include any risk information. The statement "Please see . . . Important Safety Information including Boxed Warnings . . . on reverse side" included in small type in the lower left corner of the flashcard did not mitigate this misleading presentation. As a result, the flashcard misleadingly suggested that Depakote and Depakote ER are safer than has been demonstrated. (Abbott Laboratories, January 22, 2009)

A journal ad for Sanctura® (trospium chloride) 20 mg Tablets made numerous claims, including "No known metabolic drug interactions." This claim was misleading because it presented positive information concerning drug-drug interactions but omitted material risk information associated with drug interactions with other anticholinergic agents. The journal ad therefore misleadingly suggested that Sanctura is safer than has been demonstrated by substantial evidence or substantial clinical experience. Inclusion of a bolded, boxed reference stating "Please see accompanying Brief Summary of full Prescribing Information" was not sufficient to provide appropriate qualification or pertinent information for the claims made in the piece. The journal ad also failed to communicate pertinent risks, such as commonly experienced adverse events associated with Sanctura (i.e., dry mouth, constipation, and headache). The omission of these risks was exacerbated by the claim in the ad that Sanctura is "[a] safe choice" and by the fact that the journal ad failed to present risk information with a prominence and readabilty reasonably comparable to the presentation of information relating to the effectiveness of Sanctura. (Indevus Pharmaceuticals, Inc., January 27, 2009)

[1] The Advertising and Promotional Labeling Branch (APLB) in FDA's Center for Biologics Evaluation and Research (CBER) did not issue any letters in December.

Broadening of Indication/Failure to State Full Indication

A Continuum Care Pharmacy formulary flashcard for Depakote® (divalproex sodium delayed-release) Tablets and Depakote® ER (divalproex sodium extended-release) Tablets misleadingly implied that Depakote ER is indicated for use in a broader range of mania patients than Depakote, which is not the case. Specifically, the flashcard included the following claim: "Expanded acute mania indication with Depakote ER that includes mixed episodes associated with bipolar disorder, with or without psychotic features." In fact, the populations studied in the mania clinical trials of both products were selected using a broad interpretation of acute mania in bipolar disorder, and there were no clinical differences between the mania populations studied for each drug. The implication that the mania indication for Depakote ER is an "expanded" indication that offers an advantage over Depakote was misleading. Additionally, the flashcard failed to include specific indications for Depakote. The statement "Please see full Indications . . . on reverse side" in small type in the bottom left corner of the flashcard did not mitigate this omission. (Abbott Laboratories, January 22, 2009)

Omission of Material Facts

A Continuum Care Pharmacy formulary flashcard for Depakote® (divalproex sodium delayed-release) Tablets and Depakote® ER (divalproex sodium extended-release) Tablets omitted material contextual information regarding the clinical pharmacology of Depakote ER. Specifically, the flashcard presented the claim: "Smoother blood levels with fewer peaks and troughs." By presenting this claim without revealing that the clinical significance of the relationship between plasma blood concentration and clinical response is not well documented, the flashcard misleadingly suggested that Depakote ER use will offer patients some clinical benefit due to "smoother blood levels." Furthermore, the flashcard claimed that Depakote ER has "All the Benefits of Depakote With the Advantages of Extended Release." This claim was misleading because it failed to explain that Depakote ER is not bioequivalent to Depakote at equal daily doses. Rather, Depakote ER is 8-20% less bioavailable when compared to equal daily doses of Depakote. Therefore, to obtain an equivalent bioavailable dose of Depakote, the Depakote ER dose must be increased by 8-20%. By failing to include this material contextual information, the flashcard misleadingly suggested that Depakote ER offers all of the benefits of an equal dose of Depakote. (Abbott Laboratories, January 22, 2009)

Overstatement of Efficacy

A journal ad for Sanctura® (trospium chloride) 20 mg Tablets claimed: "Day 1 relief . . . ." This time-to-onset-of-effect claim was misleading because it was not supported by substantial evidence or substantial clinical experience. The reference cited for this claim is a post-hoc analysis of efficacy data from a clinical study in which patients with overactive bladder were randomized to placebo or Sanctura. The onset of action regarding urge urinary incontinence was analyzed using a reverse stepwise method, which was done retrospectively and therefore did not soundly support the claim. Moreover, the reverse stepwise analysis was performed on only one of two studies identified as "pivotal" that were submitted to the NDA. The results from the other pivotal trial showed statistical significance compared to placebo beginning on day 7. The claim that relief begins at day 1 was therefore based on a selective presentation of the most favorable data. The journal ad also misleadingly claimed: "Quality of life significantly improved." In support of this claim, the journal ad referenced the Incontinence Impact Questionnaire (IIQ). The IIQ measures the impact of overactive bladder on travel, physical activity, social relationships, and emotional health but not on other domains covered by the broad claim of "quality of life," such as work productivity and financial stability. Additionally, the study did not show

a significant improvement on all of the IIQ subscales. This reference therefore was not sufficient to support the claim that Sanctura will significantly improve patients' quality of life. (Indevus Pharmaceuticals, Inc., January 27, 2009)

Unsubstantiated Superiority Claims

A journal ad for Sanctura® (trospium chloride) 20 mg Tablets misleadingly suggested that Sanctura is superior to other drug therapies for overactive bladder (OAB). For example, the journal ad included the following claims, presented around an illustration of a large four-leaf clover surrounded by a golden halo standing above numerous three-leaf clovers: "In a world where many OAB drugs are the same . . . ONE stands out" and "Look no further." The totality of these claims and presentations misleadingly suggested that Sanctura confers more therapeutic benefits than other therapies for OAB. In addition, the presentation misleadingly suggested that Sanctura is superior to other OAB therapies based on its clinical pharmacology. While the intrinsic chemical structure (i.e., quaternary amine, represented by the four-leaf clover) of Sanctura is different from other OAB drugs, FDA is not aware of any studies demonstrating that the structure of Sanctura offers any distinct patient benefits or conveys any clinically significant advantage or any studies indicating that Sanctura is superior to other drugs for the treatment of OAB. (Indevus Pharmaceuticals, Inc., January 27, 2009)

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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