November 6, 2007

Summary of DDMAC Enforcement Correspondence October 2007

In October 2007, FDA's Division of Drug Marketing, Advertising, and Communications (DDMAC) posted one untitled letter on its website.[1] The letter addressed the issues below. This summary describes only DDMAC's allegations. It does not reflect the recipient's response or analysis by Covington & Burling.

Overstatement of Efficacy

A professional mailer for Cymbalta® (duloxetine hydrochloride) Delayed-release Capsules overstated the efficacy of the drug because it suggested that patients with diabetic peripheral neuropathy (DPN) who are treated with Cymbalta experience significantly less pain interference with overall functioning. This claim has not been demonstrated by substantial evidence or substantial clinical experience. The reference cited to support the claim does not constitute substantial evidence because it reports pooled efficacy data from multiple studies that were submitted to the new drug application (NDA) in support of findings regarding the average Brief Pain Inventory (BPI) – Interference Portion Score in patients treated with Cymbalta or placebo. The submitted studies of effects on the BPI pain interference subscale failed to demonstrate a statistically significant separation from placebo in the individual efficacy studies submitted to the NDA. Pooling the data can yield a statistically significant difference, but this post-hoc analysis is not a credible source of data. A claimed effect on the BPI – Interference Portion must be supported by a prospectively planned analysis of a study designed to test this effect.

Moreover, the studies at issue were not adequately designed to substantiate the claim of "significantly less pain interference with overall functioning." The BPI asks patients to rate their level of pain interference using seven items depicted in a chart in the promotional mailer (general activity, mood, walking ability, normal work, relationships with others, sleep, and enjoyment of life). Each of these items, however, measures a general concept that cannot be adequately captured with a single-item question. For example, patients are required to rate pain interference as it pertains to each of these general concepts by averaging their experiences across all important aspects of that general concept. In addition, each pain interference question requires patients to compare their current condition to a previous state without pain. FDA is not aware of any evidence that patient responses to such questions yield valid data. Consequently, the agency does not believe there is evidence that patients' responses are valid or reliable. (Eli Lilly and Company, September 21, 2007)

Omission of Materials Facts

A professional mailer for Cymbalta® (duloxetine hydrochloride) Delayed-release Capsules presented numerous efficacy claims, but it failed to communicate some of the most serious

[1] DDMAC did not post any letters during the month of September. The untitled letter is dated September 21, 2007, but it was not posted until October 2, 2007.

risks associated with the use of Cymbalta. Moreover, while the mailer included some information from the Boxed Warning and the Adverse Reactions sections of the package insert (PI), it failed to include other important risk information. More specifically, it failed to reveal the Contraindication regarding use in patients with uncontrolled narrow-angle glaucoma and the Contraindication and bolded Warning relating to use with monoamine oxidase inhibitors. It also failed to reveal the Precautions relating to hepatotoxicity, abrupt discontinuation of Cymbalta treatment, and use of the drug in patients with concomitant illness. The fact that the mailer contained the statement "See additional Important Safety Information and full Prescribing Information, including Boxed Warning, inside this mailer" on its middle flap and that a removable PI was located in its interior pocket did not mitigate these misleading omissions. (Eli Lilly and Company, September 21, 2007)

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