SUMMARY OF FDA ADVERTISING AND PROMOTION ENFORCEMENT ACTIVITIES

SEPTEMBER 2010

This e-alert is part of a monthly series of e-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 September 2010, FDA’s Division of Drug Marketing, Advertising, and Communications (DDMAC) posted the following two untitled letters on its website:1

- Acuvail™ (ketorolac tromethamine ophthalmic solution) 0.45%, Allergan, Inc. (August 25, 2010) 2
- Premarin® (conjugated estrogens tablets, USP), Wyeth Pharmaceuticals, Inc. (August 27, 2010)

The letters, taken together, make allegations under the following headings: Omission/Minimization of Risk Information; Overstatement of Efficacy; and Broadening of Indication. The letters conclude that the cited advertising/promotional issues render the subject products misbranded.

This alert merely summarizes the allegations contained in FDA’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.

Omission/Minimization of Risk Information

FDA’s letters contain the following allegations under an “Omission/Minimization of Risk Information” subheading:

DDMAC untitled letter to Allergan, Inc. re: Acuvail™ (ketorolac tromethamine ophthalmic solution) 0.45% (August 25, 2010) (“Allergan untitled letter”): A professional journal ad for Acuvail included the following claim: “With some NSAIDs, there exists the potential for increased bleeding due to interference with thrombocyte aggregation.” This statement failed to include related information from the “Warnings and Precautions” section of the product’s package insert (PI) regarding how this adverse event could manifest with ocular NSAID use. Specifically, it omitted that “[t]here have been reports that ocularly applied nonsteroidal anti-inflammatory drugs may cause increased bleeding of ocular tissues (including hyphemas) in conjunction with ocular surgery.” The ad also omitted the

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1 Only enforcement letters posted to FDA’s website in September 2010 are included herein. Letters issued in September but not posted to the website by September 30, 2010 will be summarized in our alerts for the months in which those letters are posted. Neither FDA’s Center for Biologics Evaluation and Research (CBER) nor the Center for Devices and Radiological Health (CDRH) posted any applicable letters on its website in September.

2 Dates referenced for the letters are issue dates.
warning and precaution that Acuvail should not be administered while a patient is wearing contact lenses.

**DDMAC untitled letter to Wyeth Pharmaceuticals, Inc. re: Premarin® (conjugated estrogens tablets, USP), Wyeth Pharmaceuticals, Inc. (August 27, 2010) ("Wyeth untitled letter"):** Patient testimonial videos located on the homepage of the Premarin website minimized the risk associated with the product by failing to convey any risk information during the audio-visual portion of the presentation. Specifically, the testimonials presented five women sharing their positive experiences with Premarin. In contrast, risk information associated with Premarin was “relegated to the bottom portion of the webpage below the testimonials in read-only text format, where it [was] unlikely to draw the viewer’s attention.” The audio-visual presentations omitted any discussion of serious risks, such as contraindications, warnings, and precautions associated with product use. Overall, this presentation failed to convey important risk information with a prominence and readability reasonably comparable to the claims of effectiveness.

**Overstatement of Efficacy**

FDA’s letters contain the following allegations under an “Overstatement of Efficacy” subheading:

**Allergan untitled letter:** A professional journal ad for Acuvail included prominent claims and graphic presentations comparing Acuvail to other NSAIDs and to the basic ketorolac molecule, suggesting that Acuvail confers more therapeutic benefits and has been “enhanced” in comparison to other such products. Although product differences exist in certain aspects of Acuvail’s chemical properties and within the composition of its solution, FDA is not aware of any substantial evidence or substantial clinical experience to support the implication that Acuvail has been “enhanced” in any way or is superior to other ocular ketorolac products or other ocular NSAIDs in treating pain and inflammation following cataract surgery, or in any other outcomes. For these reasons, the claims constitute unsubstantiated superiority claims. They also overstate the efficacy of the product. In addition to suggesting superiority over other NSAIDs, the ad contained the claim that product use would result in “[o]ptimal outcomes” and “enhanced patient comfort.” FDA is not aware of substantial evidence or substantial clinical experience to support these claims. Although the Acuvail package insert (PI) was cited in support of the patient comfort claim, FDA asserts that it does not contain any supportive evidence. On the contrary, the PI specifically states that patients using Acuvail experienced adverse events, such as ocular pain, headache, and blurred vision, which could undermine patient comfort.

**Wyeth untitled letter:** A patient testimonial video for Premarin included statements implying that Premarin will eliminate all hot flashes, discomfort, and other symptoms associated with menopause, and that the product will “circumvent being on menopause at all.” These statements “significantly exaggerate” what was demonstrated in Premarin’s clinical trials, particularly as patients taking 0.625 mg, 0.45 mg, and 0.3 mg doses of the product experienced a mean of 0.75, 2.32, and 2.52 hot flashes per day at 12 weeks, respectively. Another video included claims that implied Premarin has been shown to immediately eliminate all vaginal dryness associated with menopause. Although data from the Health and Osteoporosis, Progesterin, and Estrogen (HOPE) study was submitted to support the safety and efficacy of multiple doses of oral Premarin for the treatment of moderate to severe symptoms of vulvar and vaginal atrophy due to menopause, the study does not support the claims that Premarin will immediately eliminate all vaginal dryness. Furthermore, estrogens, including Premarin, require an interval of time to reverse the signs and symptoms of vaginal atrophy. Finally, the patient testimonials included claims implying that treatment with Premarin will improve a patient’s overall physical and emotional functioning, including “feeling very much alive” and bringing “life back into a normal balance.” FDA is not aware of substantial evidence or substantial clinical experience to support patient-reported outcomes such as these. The personal experiences of
specific patients do not constitute such evidence. On the contrary, the drug carries many potential risks that can have a significant negative impact on a patient’s overall functioning.

Broadening of Indication

FDA’s letters contain the following allegations under a “Broadening of Indication” subheading:

**Allergan untitled letter:** A professional journal ad for Acuvail included several prominent claims comparing the product to the basic ketorolac molecule and to other NSAIDs, e.g., “A new shape in NSAID therapy,” “The ketorolac molecule enhanced, the NSAID advanced,” and “Your next NSAID.” These comparisons imply that Acuvail is safe and effective for any of the approved uses of other ocular ketorolac products or other ocular NSAIDs, when this has not been demonstrated by substantial evidence or substantial clinical experience. Acuvail is indicated only for pain and inflammation following cataract surgery, and not for any of the other uses for which ocular NSAIDs are approved, such as temporary relief of pain and photophobia in patients undergoing corneal refractive surgery. Therefore, the comparison claims misleadingly broaden the indication for Acuvail. The presentation of the indication in the middle of the ad was insufficient to mitigate the misleading impression created by these claims.

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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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