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E-ALERT | Food & Drug

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SUMMARY OF FDA ADVERTISING AND PROMOTION ENFORCEMENT ACTIVITIES

MARCH 2012

This e-alert is part of a series of monthly 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 March 2012, FDA's Office of Prescription Drug Promotion (OPDP) posted the following enforcement letters on its website:[1]

- Untitled letter to Merck & Co, Inc. re: Saphris® (asenapine) sublingual tablets (February 28, 2012) ("Merck Untitled Letter")[2]
- Untitled letter to Dow Pharmaceutical Science, Inc. re: Atralin™ (tretinoin) Gel, 0.05% (March 6, 2012) ("Dow Untitled Letter")
- Untitled letter to Biogen Idec re: AVONEX® (Interferon beta-1a) IM Injection (March 14, 2012) ("Biogen Untitled Letter")
- Warning Letter to Teva Pharmaceuticals USA re: COPAXONE® (glatiramer acetate injection) solution for subcutaneous injection (March 14, 2012) ("Teva Warning Letter")

The Office of Compliance and Biologics Quality (OCBQ) in FDA's Center for Biologics Evaluation and Research (CBER) posted the following letter on FDA's website:

- Warning letter to IntelliCell Biosciences, Inc. re: IntelliCell product (March 13, 2012) ("IntelliCell Warning Letter")

During March 2012, the Office of Compliance in FDA's Center for Devices and Radiological Health (CDRH) did not post any enforcement letters relating to the advertising and promotion of medical devices. The letters posted by OPDP and OCBQ raise a variety of allegations and conclude that the cited advertising/promotional issues render the subject product misbranded and/or result in the unlawful marketing of an unapproved drug.

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.

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[1] Only enforcement letters posted to FDA's website in March 2012 are included herein. Letters issued in March but not posted to the website by March 31, 2012 will be summarized in our alerts for the months in which those letters are posted.

[2] The dates referenced for the letters are the issue dates.

Promotion of an Unapproved Use[3]

FDA's letters contain the following allegations under a "Promotion of an Unapproved Use" subheading:

Merck Untitled Letter: Saphris is indicated for the treatment of schizophrenia or for the acute treatment of manic or mixed episodes associated with bipolar I disorder, either as monotherapy or adjunctive therapy with lithium or valproate. At a Merck Peer Discussion Group luncheon on April 26, 2011, Dr. Armando Favazza, MD, speaking on behalf of Merck, made an oral statement that "misleadingly suggested that Saphris is safe and effective for use as an adjunctive treatment for MDD [major depressive disorder]." Specifically, Dr. Favazza stated that he prescribes Saphris as an adjunctive treatment for MDD just as he might prescribe Abilify,[4] and that it works just as well. The statement was reported to FDA as part of OPDP's Bad Ad Program, and OPDP found that Dr. Favazza's oral statement misbranded the drug by suggesting a new "intended use" for Saphris for which the drug's product labeling lacks adequate directions for use.

IntelliCell Warning Letter: Upon inspection of IntelliCell Biosciences, Inc., FDA determined that the company recovers and processes adipose tissue (aka lipoaspirate) from donors for autologous use. The IntelliCell product—adipose-derived stem cells—is administered to patients intravenously, or is injected into specific areas of the body, including the lips, cheeks, knees, scalp, and buttocks. A YouTube promotional video explained that the IntelliCell product can be used "off-label to treat various patient ailments," including wrinkles, osteoarthritis, and gum recessions, and for breast augmentations. According to FDA, the IntelliCell product does not qualify for regulation solely under section 361 of the Public Health Service Act and therefore is both a drug and a biological product. Because the IntelliCell product is not the subject of an approved biologics license application (BLA), and the company does not have an IND application in effect, OCBQ concluded that the IntelliCell product violated the Food, Drug, and Cosmetic Act and the Public Health Service Act.

Overstatement of Efficacy

FDA's letters contain the following allegations under an "Overstatement of Efficacy" subheading:

Dow Untitled Letter: According to its package insert (PI), Atralin Gel is indicated for the topical treatment of acne vulgaris. Dow's direct-to-consumer website for Atralin Gel claimed that "many dermatologists prescribe a tretinoin because it works so well—even on tough acne . . . ."[5] As stated in the Clinical Studies section of the PI, the safety and efficacy of Atralin Gel was studied in patients with mild to moderate acne vulgaris only. OPDP concluded that the website's claim that the drug had been specifically studied for the treatment of "tough" or severe acne misleadingly suggested that the drug was effective in treating severe acne when this is not supported by substantial evidence.

Additionally, OPDP found that a detail aid selectively presented more favorable lesion reduction data from the registration trials while failing to include less favorable Global Severity Score Success data, which measured overall acne severity and was a primary trial endpoint. The omission of this less favorable data led OPDP to conclude that the detail aid overstated the efficacy of Atralin Gel.

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[3] The IntelliCell Warning Letter issued by OCBQ does not explicitly use this subheading, but the allegations fit within this category.

[4] Abilify is an atypical antipsychotic with several approved indications, including the adjunctive treatment of major depressive disorder.

[5] Emphasis added by OPDP.

Biogen Untitled Letter: Avonex is indicated for "treatment of patients with relapsing forms of multiple sclerosis to slow the accumulation of physical disability and decrease the frequency of clinical exacerbations." As part of its Avonex consumer website, Biogen Idec's webpage "Long Term Results" included various claims and presentations, including (emphasis in original):

- "**AVONEX may help you stay active and able longer** . . . In a long-term follow up study, **8 out of 10** people taking AVONEX had an [Expanded Disability Status Scale] EDSS score below **3.0 at 10 years**, which means they were still active and able."
- A pictorial representation of the EDSS and the claim, "**80% below EDSS 3.0 at 10 years**."

OPDP found that the webpage misleadingly overstated the efficacy of Avonex. As OPDP explained, the study cited on the webpage is a 10-year, open-label, follow-up study that is not an adequate and well-controlled clinical study constituting substantial evidence of long-term efficacy. Further, the clinical studies included in Avonex's PI support the efficacy of the drug for up to three years in duration only. Finally, the presentation implied that the drug is effective for each of the individual functional areas of the EDSS listed on the webpage.[6] FDA was not aware of substantial evidence or substantial clinical experience to support this implication.

Teva Warning Letter: Copaxone is indicated for "reduction of the frequency of relapses in patients with Relapsing-Remitting Multiple Sclerosis (RRMS), including patients who have experienced a first clinical episode and have MRI features consistent with multiple sclerosis." Professional exhibit panels for a 2011 meeting of the American Academy of Neurology (AAN) included claims such as:

- **"20 years of proven safety."**
- **"Expanded Disability Status Scale (EDSS) scored remained stable after an average of 15 years on therapy."**[7]

According to OPDP, these claims misleadingly implied that the drug has proven long-term (e.g., 20 years, 15 years, etc.) safety and efficacy, even though the Clinical Studies section of the drug's PI includes data for up to three years duration only. The open-label extension studies referenced in the AAN exhibit panels do not constitute substantial evidence to support these claims, and thus the panels overstated the safety and efficacy of Copaxone.

Additionally, OPDP concluded that claims on several webpages for Copaxone misleadingly suggested the drug is more effective or useful in a broader range of conditions or patients than has been demonstrated by substantial evidence or substantial clinical experience. For example, the "David Kyle" webpage stated that he had been diagnosed with multiple sclerosis (MS) in 2002 and had to use a cane for mobility. After starting Copaxone therapy in 2003, however, "David went on to compete and win numerous national and international triathlons from 2005-2008." Further, the "Karen Stewart" webpage indicated that she had experienced numbness in her leg and optic neuritis, and she eventually could no longer walk unassisted and was forced to leave her job. Karen began taking Copaxone in 1998, and she now "exercises six days a week, added Pilates to her exercise regimen and continues to work as a registered nurse (RN). To date, Karen has walked 22 marathons . . . ."

According to OPDP, these claims implied that "Copaxone reverses patients' disability and enables them to lead an active lifestyle, return to work, accomplish great athletic feats, and 'live the life they've dreamed.'" Copaxone is not indicated for slowing, preventing, or reversing physical disability

[6] EDSS areas listed on the webpage include: brain function, coordination skills, bowel and bladder function, sensory and motor symptoms, visual symptoms, and ability to walk.
[7] Underline emphasis added by OPDP.

associated with RRMS, and the inclusion of the dates 1998 and 2003 implies that the drug is effective for reducing the frequency of relapses or exacerbations beyond the time period (three years) established in the Clinical Studies section of the PI for Copaxone. Additionally, OPDP concluded that these presentations implied that Copaxone is approved to treat all types of MS when, in fact, Copaxone is indicated only for the reduction of the frequency of relapses in patients with RRMS. OPDP found similar overstatements of efficacy that broadened the indication for the drug on the "Team COPAXONE®" webpage, and in the AAN exhibit panels.

Unsubstantiated Superiority Claims

FDA's letters contain the following allegations under an "Unsubstantiated Superiority Claims" subheading:

Dow Untitled Letter: According to OPDP, both Dow's direct-to-consumer website and a detail aid made misleading claims as to Atralin Gel's superiority over other tretinoin formulations. For example, the website claimed that, "unlike other acne medications, ATRALIN™ Gel is the only tretinoin formulation that features a unique combination of ingredients that are known to moisturize and hydrate skin."[8] The detail aid made similar claims regarding the specific clinical benefits of Atralin Gel's vehicle. OPDP found that these superiority claims were not supported by substantial evidence nor substantial clinical experience, and pointed to the Description section of Atralin Gel's PI, which states "the contribution to efficacy of individual components of the vehicle has not been evaluated," and the Adverse Reactions section, which states that 16% of patients who used the drug experienced dry skin.

Further, OPDP addressed various claims and presentations in the detail aid, including:

- "At" in the tradename circled and appearing to look like "A+".
- "Uniquely formulated for targeted delivery" along with claims of the purported benefits of the drug's micronized formulation.
- "A smart combination for improved tolerability" along with claims of the purported benefits of ingredients in the drug's vehicle and an "A+" graphic.
- "Superior delivery" along with a graph of *in vitro* data showing Atralin Gel with the greatest mean cumulative level of tretinoin to the dermis at 24 hours compared to Retin-A Micro® 0.1% gel and Retin-A Micro® 0.04% gel. A footnote to the graph stated: "In vitro data; clinical significance is unknown. Differences between products were not statistically significant."

OPDP concluded that these claims misleadingly suggested that Atralin's formulation and its purported targeted delivery to the dermis result in superior safety and efficacy compared to other tretinoin products, because FDA was not aware of any substantial evidence supporting these superiority claims. Additionally, as to the *in vitro* data, OPDP stated that this method was not adequate for assessing comparative *in vivo* levels clinically at the dermis for different formulations, due to the physiological difference between healthy skin (used in the *in vitro* absorption testing) and diseased skin. According to OPDP, the footnote to the graph did not correct this misleading impression.

Teva Warning Letter: The 2011 AAN professional exhibit panels claimed, "**No other RRMS therapy can demonstrate long-term results like COPAXONE®**."[9] OPDP concluded that this statement misleadingly suggested that Copaxone is superior to other RRMS therapies when there is no data to support this claim.

[8] Emphasis in original.
[9] Underline emphasis added by OPDP.

Unsubstantiated Claims

FDA's letters contain the following allegations under an "Unsubstantiated Claims" subheading:

Dow Untitled Letter: OPDP found that both the detail aid and the website for Atralin Gel contained misleading, unsubstantiated claims. The detail aid included a schematic of Atralin Gel entering a follicle and included claims such as, "[m]icronized tretinoin facilitates efficient delivery to the follicle," and "[m]icronized tretinoin particles in Atralin Gel are small enough to easily enter the follicular opening." OPDP concluded that the claims and schematic misleadingly suggested that Atralin Gel's micronized formulation confers a beneficial effect by enabling the majority of tretinoin particles to enter follicles, when this has not been demonstrated by substantial evidence. Additionally, OPDP found that a claim on Atralin Gel's website that suggested patients will experience an improvement in satisfaction with their self-appearance after using the drug was not supported by the referenced study, which had failed to demonstrate any significant difference between treatment groups in the relevant self-appearance domains.

Omission of Material Information

FDA's letters contain the following allegations under an "Omission of Material Information" subheading:

Biogen Untitled Letter: OPDP concluded that through the omission of information, the claims and presentations on Avonex's "Multiple Sclerosis Treatments" webpage misleadingly implied that Avonex is superior to Copaxone, Rebif, Betaseron, and Extavia. Although a chart on the website included information consistent with Avonex's PI (i.e., that Avonex, *inter alia*, slows physical disability, reduces flare-ups, works after the first attack, and is associated with fewer doses per year), the chart failed to present information about Avonex's contraindications, warning and precautions, and laboratory test monitoring. The omission of this material information misleadingly implied that Avonex is superior, and OPDP explained that the safety information in small font at the bottom of the webpage did not mitigate this misleading implication.

Teva Warning Letter: OPDP concluded that the AAN exhibit panels omitted material facts regarding the actual relapse rates for Copaxone and placebo, and misleadingly implied a greater reduction in relapse rates than that demonstrated in the Clinical Studies section of the PI for Copaxone.

Omission and Minimization of Risk Information

FDA's letters contain the following allegations under an "Omission and Minimization of Risk Information" subheading:

Dow Untitled Letter: The direct-to-consumer website for Atralin Gel made claims including: "ATRALIN™ Gel offers a low potential for irritation. Chances are you'll stick with your treatment if there's less risk of irritation, which will help you get the best results." OPDP determined that this and similar claims misleadingly minimized the risks of Atralin Gel, and omitted material facts about the possible duration and/or severity of skin-related adverse reactions and the potential need for discontinuation of the drug. The warnings and precautions associated with Atralin Gel include skin irritation. The most common adverse reactions associated with the drug include dry skin, peeling/scaling/flaking skin, skin burning sensation, and erythema. Further, the Adverse Reactions section of the PI indicates that, in some subjects, the skin-related adverse reactions persisted throughout the treatment period. Additionally, both the website and detail aid omitted any warning or precaution regarding use of the drug in patients with fish allergies.

Teva Warning Letter: The AAN exhibit panels contained a table that listed three risks associated with Copaxone, and numerous risks not associated with Copaxone, including immunosuppression/infections, decrease in pulmonary function, and anaphylaxis/hypersensitivity. OPDP determined that this presentation misleadingly implied that Copaxone is safer than other treatments for RRMS because it is not associated with serious risks generally attributed to other RRMS drugs. According to OPDP, "this is not the case. While we acknowledge that the PI for Copaxone does not have these risks listed in the WARNINGS AND PRECAUTIONS section, it does not mean that such risks are not associated with the drug." In fact, according to the PI, infection, influenza, and hypersensitivity were reported in clinical trials for Copaxone at a rate higher than that of the placebo group.

OPDP determined that this presentation omitted material information, which minimized the risk of Copaxone and implied that the drug is safer and superior to other treatments for RRMS. For example, the presentation failed to present warnings for chest pain and skin necrosis, and the risk of injection site reactions, such as erythema, pain, edema, and hypersensitivity. Further, the AAN exhibit panels claimed that "**NO initial or routine monitoring required or recommended**,"[10] and indicated that this was recommended in INFβ, natalizumab, and fingolimod. According to OPDP, "without a comparison of other attributes associated with the product, or, potentially other material facts that may be necessary within the context of a comparative presentation, the exhibit panels misleadingly suggest that Copaxone is a safer, better, or otherwise superior treatment option for RRMS."

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[10] Emphasis in original.