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E-ALERT | Food & Drug

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SUMMARY OF FDA ADVERTISING AND PROMOTION ENFORCEMENT ACTIVITIES

JUNE 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 June 2010, FDA's Division of Drug Marketing, Advertising, and Communications (DDMAC) posted the following five enforcement letters (all untitled) on its website:[1]

- Gliadel® Wafer (polifeprosan 20 with carmustine implant), Eisai Corporation of North America (May 27, 2010)[2]
- Lunesta® (eszopiclone) Tablets, Sepracor, Inc. (June 9, 2010)
- XIAFLEX™ (collagenase clostridium histolyticum) for injection, for intralesional use, Auxilium Pharmaceuticals, Inc. (June 10, 2010)
- ACETADOTE® (acetylcysteine) Injection, Cumberland Pharmaceuticals Inc. (June 14, 2010)
- Intuniv™ (guanfacine) extended-release tablets, Shire Development, Inc. (June 22, 2010)

The letters address the following issues: Omission/Minimization of Risk, Overstatement of Efficacy, Unsubstantiated Superiority Claims, Omission of Material Facts, Broadening of Indication, and Unsubstantiated Claims. DDMAC's letters conclude that the cited advertising/promotional issues render the subject product misbranded.

This alert merely summarizes the allegations contained in DDMAC'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 during June 2010 are included herein. Letters issued in June but not posted to the website by June 30, 2010 will be summarized in our alerts for the months in which those letters are posted. As of the date of publication of this alert, the following additional letter, issued in June, has been posted on the DDMAC website: Untitled Letter to Cornerstone Therapeutics, Inc. re: Zyflo CR (zileuton) extended-release tablets (issued June 22, 2010, posted July 1, 2010). Neither the Advertising and Promotional Labeling Branch (APLB) in FDA's Center for Biologics Evaluation and Research nor the Center for Devices and Radiological Health (CDRH) posted any applicable letters on its website in June.

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

Omission/Minimization of Risk Information

FDA's letters contain several allegations under an "Omission/Minimization of Risk Information" subheading. These include:

DDMAC untitled letter to Eisai Corporation of North America (May 27, 2010) ("Eisai untitled letter"): A consumer-directed video for Gliadel Wafer failed to present information about risks associated with the drug with a prominence and readability reasonably comparable to the efficacy presentation. Specifically, the video minimized the risks of Gliadel by failing to "convey **any** of the serious risks of Gliadel during the audiovisual portion of the video." The first 4 minutes and 15 seconds of the video were devoted to a description of primary brain tumors, the mechanism of action of Gliadel, and promotional statements about the drug's benefits presented in graphic and audio fashion. In contrast, the presentation of the drug's serious risks was "relegated to the end of the video" following several cues suggesting the video had finished, where it was "unlikely to draw the viewer's attention." Although a running telescript with accompanying voiceover of Gliadel's indication, contraindications, and warnings appeared at the end of the video, this presentation lacked comparable prominence to the benefit claims. This issue was exacerbated by the fact that the video "entirely omit[ted] any discussion of the precautions and adverse reactions associated with Gliadel."

DDMAC untitled letter to Auxilium Pharmaceuticals, Inc. (Jun. 10, 2010) ("Auxilium untitled letter"): A direct-to-consumer (DTC) patient brochure for Xiaflex included presentations of risk information that suggest Xiaflex is safer than has been demonstrated, thereby minimizing the risks associated with the drug. For example, under the heading "XIAFLEX Side Effects and Safety," the brochure included a statement that the most common side effects are "generally mild or moderate and usually resolve within 4 weeks with no additional treatment." FDA is not aware of substantial evidence to support the claim that the most common side effects are "mild or moderate" and this characterization served to minimize the severity and frequency of the drug's common adverse reactions. According to the package insert (PI), the drug is associated with painful common adverse reactions, and up to 98% of Xiaflex-treated patients in clinical trials had an adverse reaction. In addition, serious risks were placed under the headline "**Other Side Effects**" at the bottom of a page. The placement of the serious risks under this headline at the bottom of the page served to further minimize the presentation of risk information by failing to give readers a clear signal that the information presented in this location related to the serious side effects Xiaflex can cause.

DDMAC untitled letter to Cumberland Pharmaceuticals, Inc. (Jun. 14, 2010) ("Cumberland untitled letter"): A professional sales aid for Acetadote included claims that minimized the risks of nausea and vomiting associated with the drug. The claims implied that treatment with Acetadote results in the "absence of emesis" and that adverse reactions of nausea and vomiting occur exclusively due to the taste and smell of orally administered acetylcysteine, and therefore would not be expected to occur with intravenously administered Acetadote. According to the package insert (PI), however, in the 15-minute loading dose regimen, 6% of patients experienced moderate nausea and 10% experienced vomiting. With the 60-minute loading dose, the incidences were 1% and 6%, respectively. Furthermore, the sales aid omitted "material information" about risks associated with Acetadote. Although the sales aid contained an "Important Safety Information" presentation, it failed to disclose "important" information regarding serious anaphylactoid reactions, including the symptoms that should be treated as anaphylactoid reactions and the steps that should be taken in response to such reactions. It also failed to disclose the most frequently reported adverse events associated with the drug.

DDMAC untitled letter to Shire Development, Inc. (Jun. 22, 2010) ("Shire untitled letter"): Several direct-to-consumer (DTC) promotional pieces for Intuniv included an "Important Safety Information" section that stated, "Do not give INTUNIV to your child if your child is allergic to guanfacine or

anything else in INTUNIV." This section, however, failed to communicate other "important risk information" from the WARNINGS AND PRECAUTIONS section of the package insert (PI). For example, it failed to note that Intuniv should also not be used concomitantly in patients taking other guanfacine-containing products (e.g., Tenex®). Additionally, various sections of the promotional materials each made promotional claims but failed to include risk information necessary to qualify these claims. For instance, an 8-page waiting room brochure presented numerous efficacy claims in the first seven pages of the piece, but failed to convey "**any** risk information specific to Intuniv" on these pages. The only specific risk information was "relegated to the back cover of the brochure." Similarly, the front side of a brochure holder presented effectiveness claims for Intuniv, but failed to communicate any risk information associated with its use. Rather, the risk information was printed on the back side of the piece where it was "unlikely to draw the reader's attention." Inclusion of the statement, "Please see Important Safety Information on back panel [or cover] and accompanying Full Prescribing Information" on the front side of the brochure holder and brochure did not mitigate the misleading omission of risk information. Moreover, the DTC promotional materials further minimized the risks of the drug by failing to present risk information with a prominence and readability reasonably comparable with the effectiveness claims. Specifically, the materials used large and colorful headers to highlight benefits of Intuniv therapy, including a prominent and compelling image of a child in a large monster suit. The risk information, however, appeared in small font and in single-spaced paragraph format, and in many cases appeared only at the end of each piece.

Overstatement of Efficacy

FDA's letters contain several allegations under an "Overstatement of Efficacy" subheading. These include:

Eisai untitled letter: The consumer-directed video for Gliadel contained claims that represented or suggested that the drug is more effective than has been demonstrated by substantial evidence or substantial clinical experience. The video contained statements implying that the drug's pharmacological properties have been shown to have a clinically significant effect by providing a chemotherapy dose 1000 times higher than systemic chemotherapy and that the carmustine in Gliadel is released in a specific dose over a specific period of time. The package insert (PI) for Gliadel states: "The absorption, distribution, metabolism, and excretion of the copolymer in humans **is unknown**. Carmustine concentrations delivered by GLIADEL® Wafer in human brain tissue **have not been determined**. Plasma levels of carmustine after GLIADEL® Wafer implant **were not determined**." (emphasis added by DDMAC). FDA is unaware of studies substantiating the claimed tissue concentrations of carmustine surrounding the Gliadel implant over a specified period of time.

Auxilium untitled letter: The DTC patient brochure for Xiaflex included claims that misleadingly overstated the efficacy of the drug. Claims such as "XIAFLEX™ treatment eliminates contracture in up to two-thirds of patients" implied that Xiaflex can permanently "eliminate" contracture, when this has not been demonstrated by substantial evidence or substantial clinical experience. Dupuytren's contracture is an incurable disease that reoccurs after treatment, including after Xiaflex injections. Additionally, the brochure claim was based on the selective presentation of only the most favorable efficacy results from one of the two clinical studies evaluating Xiaflex. In Study 1, 64% of patients achieved a specific reduction in contracture, but in Study 2, only 44% of patients achieved such a reduction. The patient brochure also contained presentations about the consequences of Dupuytren's disease progression, including its impact on the use of one's hand, daily activities, and everyday tasks. Although the patient brochure did not directly assert that Xiaflex will correct these problems, the totality of the claims, when evaluated in the context of the brochure as a whole, implied that Xiaflex treatment can reduce the likelihood or severity of disease progression or its consequences. FDA is not aware of substantial evidence or substantial clinical experience to

support such implications. In Xiaflex clinical studies, the primary efficacy endpoints were all measures that assessed the change in the degree of contracture. Although Xiaflex treatment demonstrated a reduction in contracture of the selected primary joint in a greater proportion of patients compared to placebo, FDA is unaware of studies demonstrating that this reduction in contracture corresponds with the suggested overall improvement in a patient's hand function or general activities of daily living.

Cumberland untitled letter: The sales aid for Acetadote included claims such as, "For maximal protection against hepatic injury – administer ACETADOTE within 8-10 hours post-ingestion." This claim is misleading because it indicates that maximum efficacy can be reached when Acetadote is administered in this manner even though this has not been demonstrated by substantial evidence or substantial clinical experience. Rather, the package insert (PI) states the following: "The critical ingestion-treatment interval for **maximal protection** against severe hepatic injury is between 0 – **8 hours**. Efficacy **diminishes progressively after 8 hours** and treatment initiation between 15 and 24 hours post-ingestion of acetaminophen yields limited efficacy." (emphasis added by DDMAC).

Shire untitled letter: Various DTC promotional materials for Intuniv represented or suggested that the drug is more effective than has been demonstrated by substantial evidence or substantial clinical experience. The materials included claims and presentations that emphasized individual symptoms of Attention Deficit Hyperactivity Disorder (ADHD), e.g., "**INTUNIV has been studied across a range of symptoms, including…Arguing with adults, Irritability, Temper outbursts,** [and] **Deliberately annoying others**…." The overall impression conveyed by such claims and presentations is that treatment with Intuniv will improve individual behavior problems in children with ADHD that "the whole family can see." FDA is not aware of substantial evidence or substantial clinical experience to support this implication. According to the CLINICAL STUDIES section of the package insert (PI), the efficacy of Intuniv in the treatment of ADHD was established in two placebo-controlled trials in children and adolescents ages 6-17. In both studies, the primary outcome was the change from baseline to endpoint in mean ADHD Rating Scale-IV (ADHD-RS). The ADHD-RS is a scale comprised of 18 clinician-rated items designed to assess ADHD's core symptoms, which are stated in Intuniv's indication. Although Intuniv showed statistically significant improvement in mean ADHD-RS score versus placebo, this scale does not measure behavioral problems such as "irritability," "arguing with adults," "temper outbursts," or "deliberately annoying others." Nor are these behavioral problems symptoms specific to ADHD. Moreover, one of the materials—a parent's guide—referenced rating scales that were not used to measure the efficacy of Intuniv in treating ADHD. Therefore, claims that implied improvements in individual components of these scales were misleading. Furthermore, the parent's guide referenced symptom improvement "**day and night**," suggesting that Intuniv is efficacious for a full 24-hour day. FDA is not aware of substantial evidence or substantial clinical experience to support this claim.

Unsubstantiated Superiority Claims

FDA's letters contain several allegations under an "Unsubstantiated Superiority Claims" subheading. These include:

DDMAC untitled letter to Sepracor, Inc. (Jun. 9, 2010) ("Sepracor untitled letter"): A DTC broadcast television advertisement for Lunesta included claims that represented or suggested that the drug is safer or more effective than another drug, when this has not been demonstrated by substantial evidence or substantial clinical experience. Various claims misleadingly implied that Lunesta is clinically superior to other medications for the treatment of insomnia and that Lunesta will be an effective sleep medication in situations where treatment with other medications has failed. For example, the voiceover in the DTC ad stated: "Ask your doctor about switching to Lunesta and

discover a restful Lunesta night." FDA is not aware of substantial evidence or substantial clinical experience to support such implications.

Cumberland untitled letter: The sales aid for Acetadote contained claims and presentations implying superiority of the drug to oral N-acetylcysteine (NAC) therapy. Specifically, the totality of the claims and presentations implied that Acetadote is more efficacious than oral NAC and that Acetadote prevents time loss and completely prevents emesis. None of these implications is supported by substantial evidence or substantial clinical experience. One of the references cited as claim support was a review article of an open label study of 25 patients treated with IV NAC and a historical control group of 29 patients treated with oral NAC only. According to DDMAC, such a study is "strongly subject to the introduction of bias." Furthermore, certain data that appeared in the sales aid could not accurately be drawn from the information provided in the reference article. Additionally, the open label study in the reference was conducted 14-24 years ago, while the historical control study was conducted 14-21 years ago. Therefore, these data may not represent current practice patterns. In general, superiority claims "should be supported by two adequate and well-controlled head-to-head clinical trials." Although certain claims in the sales aid regarding the length of treatment and number of doses for Acetadote were accurate, when presented in conjunction with the other claims in the sales aid regarding oral NAC they contributed to the misleading impression that Acetadote is superior to oral NAC. The sales aid also contained pharmacoeconomic claims such as "**Reduced treatment time for reduced treatment costs**," that the cited reference was not adequately designed to support. The cited reference assumed equivalent effectiveness between the two treatment alternatives, when there were no data in the reference to support such an assumption. Absent substantial evidence of equivalent effectiveness, the validity of the treatment cost comparisons could not be established.

Shire untitled letter: Various DTC promotional materials for Intuniv included claims or presentations that emphasized the "difference" between Intuniv and other ADHD medications, e.g., "Now there's a medicine that's different – one that has been shown to improve a range of symptoms of ADHD that can be disruptive at home and at school. **Introducing INTUNIV.**" Such claims and presentations misleadingly implied that Intuniv is more efficacious than other ADHD medications in that it improves a range of symptoms that other ADHD medications do not treat, including specifically listed behavioral symptoms. FDA is not aware of any adequate and well-controlled head-to-head clinical trials demonstrating an advantage over other ADHD medications. Furthermore, as discussed above, FDA is not aware of support for the implication that Intuniv improves individual behavioral problems in children.

Omission of Material Facts

FDA's letters contain several allegations under an "Omission of Material Facts" subheading. These include:

Auxilium untitled letter: The DTC patient brochure for Xiaflex included presentations describing the administration of the drug and what to expect from drug treatment that "omit[ted] important contextual information" regarding Xiaflex. Specifically, the presentations "strongly impl[ied]" that treatment with Xiaflex is "likely to consist of a **single** injection when, in fact, the drug is injected three times during each injection procedure on a single day, and multiple injection procedures may be needed." Furthermore, the presentation suggested that the claimed efficacy results (elimination in contracture in up to two-thirds of patients) occur after a single injection. According to the package insert (PI), the claimed results were evaluated 30 days after the last administration of Xiaflex on the joint on days 30, 60, or 90 (i.e., on 3 separate days). Therefore, these results included patients who had to return for additional follow-up injection procedures, are not representative of what patients

can expect after a single injection procedure, and reflect a selective presentation of only the most favorable clinical trial information.

Cumberland untitled letter: The sales aid for Acetadote included the Rumack-Matthew Nomogram, followed by a chart listing Plasma or Serum APAP Concentrations, Risk of Hepatotoxicity, and Action (administer or discontinue Acetadote). The totality of the presentation was misleading because it failed to reveal "material information" from the Indications and Usage section of Acetadote's package insert (PI). Specifically, the PI clearly states that the Rumack-Matthew Nomogram does not apply to patients with Repeated Supratherapeutic Ingestion (RSI), a fact which is not disclosed in the sales aid.

Broadening of Indication

FDA's letters contain the following allegations under a "Broadening of Indication" subheading:

Auxilium untitled letter: The DTC patient brochure for Xiaflex contained claims such as "FOR THE TREATMENT OF DUPUYTREN'S CONTRACTURE" and "XIAFLEX™ is the only FDA-approved nonsurgical treatment for Dupuytren's contracture," which misleadingly suggested that Xiaflex is indicated to treat all patients with Dupuytren's disease, including patients with early Dupuytren's disease without a palpable cord. However, Xiaflex is "**only** approved to treat adult patients with Dupuytren's contracture with a palpable cord." The implication that Xiaflex is appropriate for any patient with this condition misleadingly broadened the drug's indication. Although the brochure contained the statement that Xiaflex is for "adults with Dupuytren's contracture with a cord that can be felt," this was not sufficient to mitigate the overall misleading impression created by other statements prominently presented earlier in the brochure.

Unsubstantiated Claims

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

Sepracor untitled letter: The DTC ad for Lunesta included the following claim: "Lunesta is different. It keys into receptors that support sleep, setting your sleep process in motion." This claim was misleading because it implied a greater degree of certainty about the mechanism of action of Lunesta than is supported by substantial evidence or substantial clinical experience. The Pharmacodynamics section of the package insert (PI) states: "**The precise mechanism of action of eszopiclone as a hypnotic is unknown**, but its effect is believed to result from its interaction with GABA-receptor complexes at binding domains located close to or allosterically coupled to benzodiazepine receptors." (emphasis added by DDMAC). Furthermore, the claim was misleading because it implied that Lunesta's mechanism of action is "specific for and *only* affects the sleep-cycle when this is not the case." Lunesta also carries many potential risks for serious adverse effects, including the potential for abuse or dependence.

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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:

Ellen Flannery	202.662.5484	eflannery@cov.com
Richard Kingham	202.662.5268	rkingham@cov.com
Peter Safir	202.662.5162	psafir@cov.com
Michael Labson	202.662.5220	mlabson@cov.com
Erika Lietzan	202.662.5165	elietzan@cov.com
Scott Cunningham	202.662.5275	scunningham@cov.com
Scott Danzis	202.662.5209	sdanzis@cov.com
Elizabeth Jungman	202.662.5327	ejungman@cov.com
Stefanie Doebler	202.662.5271	sdoebler@cov.com
Alissa Jijon	202.662.5341	ajijon@cov.com