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Full Issue

Cephalon Settles Off-Label Drug Marketing Suits for $444 Million

Cephalon has agreed to a $444 million settlement of federal and state investigations in which officials accuse it of off-label marketing of three drugs.

The company, the Justice Department, the U.S. Attorney's Office for the Eastern District of Pennsylvania and other federal agencies announced Monday that the company had finalized an agreement it made last November (*DID*, Nov. 12, 2007).

The company will pay $375 million in fines and an estimated $12 million in interest to settle federal False Claims Act charges that it marketed Actiq (fentanyl citrate), Gabitril (tiagabine HCl) and Provigil (modafinil) for off-label uses, according to the settlement agreement. Justice's announcement accuses the company of employing measures such as:

- Training its sales force to disregard restrictions on the label for Actiq, which was approved to treat opioid-tolerant cancer patients. That led the sales staff to promote the cancer-pain drug for other uses and to physicians who were not oncologists;
- Promoting Gabitril, approved to treat partial seizures due to epilepsy, to psychiatrists to treat anxiety and other psychiatric conditions; and
- Funding continuing education programs to promote off-label uses of its drugs in violation of FDA regulations.

The civil settlement resolves four whistle-blower actions, three of which were filed by former Cephalon sales representatives. The whistle-blowers will get a total of roughly $46 million as their share of the federal settlement.

The company also will pay $50 million — $40 million in criminal fines and $10 million "applied as substitute assets" — and entered a guilty plea to a misdemeanor charge of selling misbranded drugs in interstate commerce, according to a federal agreement.

Cephalon also settled two state investigations for a total of $6.85 million, according to the company's statement, paying $6.15 million in a settlement with the Connecticut attorney general and state Commissioner of Consumer Protection and $700,000 in a settlement with the Massachusetts attorney general.

The company has entered a five-year corporate integrity agreement.

The settlement agreement is available at www.fdanews.com/ext/files/Settlement%20Agreement.pdf, the guilty plea agreement is available at www.fdanews.com/ext/files/Plea%20Agreement.pdf and the Justice Department's announcement is available at www.fdanews.com/ext/files/Justice%20Announcement.pdf. — David Grant

Statin Use Doesn't Increase ALS Risk, FDA Says

The use of cholesterol-lowering statins does not increase the incidence of amyotrophic lateral sclerosis (ALS), also called Lou Gehrig's disease, the FDA says.

Data from 41 long-term controlled clinical trials show that nine of approximately 64,000 patients treated with a statin and 10 of approximately 56,000 patients treated with placebo were diagnosed with ALS, the agency says. The results show the incidence of ALS in patients treated with statins was 4.2 cases per 100,000 patient-years compared with five cases per 100,000 patient-years for those on placebo.

The analysis, which appears in *Pharmacoepidemiology and Drug Safety*, was undertaken in 2007 after the FDA received a higher-than-expected number of adverse event reports of patients on statins developing ALS.

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In a joint session last year, the FDA's Nonprescription Drugs and Endocrinologic and Metabolic Drugs Advisory Committees said there was not enough evidence linking statins and the development of Lou Gehrig's disease to warrant consideration in an approval decision regarding OTC versions of the drugs (*DID,* Dec. 17, 2007).

"Statins have also been shown to reduce the risk of heart disease in a wide variety of patients," the FDA says. "Based on currently available information, healthcare professionals should not change their prescribing practices for statins and patients should not change their use of statins."

The analysis can be viewed at www3.interscience.wiley.com/journal/121395851/abstract. — Martin Gidron

Adderall XR Video on YouTube Prompts FDA Warning

The FDA cited Shire Pharmaceuticals in a warning letter about a video posted on YouTube.com that featured ABC's "Extreme Makeover: Home Edition" star Ty Pennington speaking about his positive experiences with Adderall XR, a treatment for attention deficit hyperactivity disorder (ADHD).

Pennington says in the video that medicines such as Adderall XR (mixed amphetamine salts) gave him the confidence to achieve his goals, according to the letter.

"These claims imply an impact on aspects of a patient's life that are much broader than those actually impacted by Adderall XR treatment," the FDA says in the letter. "Furthermore, the video overstates the efficacy of Adderall XR by implying that Adderall XR will help patients overcome communication difficulties and help them to 'fit in' and not feel 'different' or 'alienated.'"

The company also failed to submit an FDA Form 2253 to the Division of Drug Marketing, Advertising and Communications for the video as required by 21 CFR 314.81(b)(3)(i).

The FDA says that although the product has been proven effective in clinical trials, the data do not demonstrate the "amazing transformation" claim. In addition to the efficacy claims, the agency says the video did not include any risk information.

Shire told *DID* the video had been removed from all company-managed websites. The company said the video was posted on YouTube in error — an emarketing subcontractor either did not understand the company's directions or Shire failed to communicate effectively with the firm.

The video was intended to be posted only on a Shire website that clearly disseminates risk information about the product. The YouTube webpage was supposed to have carried a link to Shire's page.

Shire received a letter of inquiry from the FDA about the video in May, and the video was removed from the YouTube website May 10, the company said.

Adderall Webpage Cited

The FDA also says a webpage on the Adderall XR site is violative because it lists statistics regarding the health consequences of untreated ADHD in an inappropriate manner.

One of the statements on the site says, "As many as 40 percent of teens with ADHD also have conduct disorder (CD), a condition linked with bullying, physical cruelty, use of weapons and other behaviors that can put them in trouble with the law." That statement was made under a section of the webpage labeled impulsive behavior.

"This presentation … broadens the indication for Adderall XR," the FDA says. "The presentation … is misleading because it suggests that Adderall XR is effective for use in treating patients with conduct disorder, when in fact, Adderall XR is not indicated for the treatment of conduct disorder, which is a distinct condition from ADHD."

The FDA asks the company to remove the cited materials from the website. However, Shire has not removed the ADHD statistics from the webpage, and it says the use of such disease-consequence claims will be the subject of its response to the FDA.

Shire told *DID* it was committed to complying with the spirit and intent of regulations covering prescription drug advertising, and it will work with the FDA to ensure the agency's concerns are addressed.

The Sept. 25 warning letter was one of five regulatory letters sent last week to ADHD drugmakers (*see related story*). The letter to Shire can be accessed at www.fda.gov/cder/warn/2008/AdderallXR_Letter.pdf. — Christopher Hollis

ADHD Drugmakers Receive Five Regulatory Letters From FDA

The FDA issued regulatory letters last week to makers of attention deficit hyperactivity disorder (ADHD) drugs for promotional materials for their products — including two warning letters and three untitled letters.

The two warning letters were issued to Eli Lilly and Shire Pharmaceuticals. The Shire letter cited the company for a promotional video featuring Ty Pennington, the star of ABC's "Extreme Makeover: Home Edition" television show (*see related story*).

The letter to Lilly cited the firm for a professional sales aid for Strattera (atomoxetine HCl). The sales aid broadens the indications for the product by presenting two graphs that show statistically significant improvement in two anxiety rating scales for patients taking Strattera, the FDA says.

"These presentations are misleading because they suggest or imply that Strattera is safe and effective for the treatment of anxiety, or, at a minimum, for the treatment of anxiety in the distinct sub-population of patients with coexisting ADHD and anxiety, when in fact, Strattera is not indicated for treatment of anxiety in either population," the FDA says in the letter.

Although a note at the bottom of the page states that Strattera is not indicated as a treatment for anxiety disorders, "this disclaimer is insufficient to mitigate the overwhelmingly misleading impression created by the piece that Strattera has been proven safe and effective for the treatment of anxiety," the FDA says.

The letter also notes that the suicidal ideation warning in physician labeling for Strattera states that anxiety has been reported in patients taking Strattera "and that there is concern that symptoms such as anxiety may represent precursors to emerging suicidal impulses," the FDA says.

After Lilly disseminated the sales aid, the company submitted a preapproval supplement to the agency regarding the tolerability of Strattera in pediatric and adult patients with ADHD and co-morbid anxiety. However, the supplement was not approved at the time the aid was released, and the aid did not include efficacy data regarding the treatment of anxiety. It just provided information regarding the use of the drug without causing a worseningof anxiety, the FDA says.

The agency also says the sales aid overstated efficacy claims by making statements and presenting statistics on the negative health outcomes due to untreated ADHD, such as increased risk of car accidents resulting from patient distraction. The agency made similar citations in Shire's warning letter.

"These presentations are misleading because they imply, in the context of the piece as a whole, that Strattera reduces the likelihood or severity of these consequences of untreated ADHD when this has not been demonstrated by substantial evidence or substantial clinical experience," the letter says.

In response to the letter, Lilly says in a statement that it discontinued the use of the sales aid in fall 2007, and some of the information in the aid was used in other promotions. "We are reviewing other promotional materials, and will revise material in response to this action," the company says.

Three Untitled Letters

Mallinckrodt, Johnson & Johnson (J&J) and Novartis each received an untitled letter citing the firms for promotions regarding their ADHD medications — Methylin (methylphenidate HCl), Concerta (methylphenidate HCl) and Focalin XR (dexmethylphenidate HCl), respectively.

The citations for Mallinckrodt's Methylin include overstating efficacy in a patient brochure by highlighting the consequences of untreated ADHD, omitting risk information by promoting the product as medication that will help patients avoid declines in appetite and making unsubstantiated comparative claims by stating that Methylin is good for patients "who are highly sensitive to medication and need a low or precise dose."

The FDA accuses J&J of overstating the efficacy of Concerta in professional convention panels saying the drug helps children improve their academic performance. One panel omitted information about the long-term suppression of growth in patients, which physician labeling cites as something that should be monitored, the letter says.

The letter to Novartis regarding Focalin XR says the company overstated the product's efficacy by presenting numerous statements in a professional slide deck on the consequences of untreated ADHD. The slide deck also broadened Focalin's indication by presenting information that indicates the product is effective for long-term use, which has not been demonstrated, the FDA says. — Christopher Hollis

Generic Preemption Case Against Purepac to Proceed

A California appeals court ruled that FDA approval of the label on Purepac's generic heartburn drug cannot preempt a case against the drugmaker, and the plaintiff can sue the company in state court for failing to warn about the drug's potential risks.

The California Fifth District Court of Appeals in Fresno found that the Superior Court of Stanislaus County erred when it concluded that plaintiff Carlyne McKenney's complaint against Purepac was preempted by FDA approval of Purepac's label on its generic Reglan (metoclopramide).

McKenney alleges that Purepac's label contained "false and/or misleading statements" about the tardive dyskinesia that she developed after taking the drug. She says in the complaint that the company "substantially understated and downplayed the risks of tardive dyskinesia," a neurological condition characterized by repetitive, involuntary movements.

Purepac contended that because the FDA cleared its metoclopramide labeling, the company cannot be found liable under state law for McKenney's injury. The company also said that being held liable under state would "stand as an obstacle to the accomplishment and execution of the full purpose and objectives of Congress." The Superior Court agreed with the company on that front.

The appeals court did not agree with the lower court finding, saying that Purepac "has not called our attention to anything in the allegations of McKenney's … complaint that would demonstrate the necessary applicability of a preemption defense to those allegations." Nothing in the "complaint alleges that Purepac should have given warnings about the use of metoclopramide that the FDA expressly precluded Purepac from giving," according to appeals court documents.

Purepac also failed to cite any appellate court decision holding that a generic manufacturer of a prescription drug can never be held strictly liable for failure to warn when the generic manufacturer uses FDA-approved labeling, according to the documents.

The court reversed the judgment against McKenney and awarded her the costs of the appeal.

Wyeth v. Levine, a case involving federal preemption, is pending before the U.S. Supreme Court. The case reached the high court when Wyeth appealed a Vermont Supreme Court decision that upheld a $6.8 million jury award to Diana Levine, who contends the label on Wyeth's anti-nausea drug Phenergan (promethazine HCl) had inadequate warnings and instructions. She lost part of her arm when the drug was administered incorrectly.

Wyeth has contended that enforcement of the Vermont state law invoked by Levine would obstruct the enforcement of the Federal Food, Drug and Cosmetic Act and FDA regulations. The court will hear that case Nov. 3. — Elizabeth Jones

ThromboGenics' Microplasmin May Restore Circulation

ThromboGenics' microplasmin helped restore blood flow within eight hours in one fourth of acute ischemic stroke patients who received the drug intravenously compared with 10 percent of those on placebo, a study suggests.

The data came from a Phase II clinical trial of 40 patients, and the trial's small size prevents the results from being statistically significant, the Belgian company says. The study did show that microplasmin-treated patients had a statistically significant improvement in the damage to the blood-brain barrier compared with placebo-treated patients.

The purpose of the trial was to evaluate safety and preliminary efficacy of microplasmin to treat stroke three to 12 hours after symptoms begin. The study showed that microplasmin was generally well tolerated with no evidence of increased bleeding risk, no systemic bleeding events and no evidence of increased rate of bleeding in general for patients on the drug. The trial results were presented at the World Stroke Congress in Vienna.

The trial was a multi-site, randomized, double-blind, placebo-controlled, ascending-dose clinical trial in which patients were enrolled four to 12 hours after onset of acute ischemic stroke. The trial investigated three-dose regimens of microplasmin (2-, 3- and 4-mg/kg total dose) compared with placebo. Patients received clinical and neurological assessments seven days and 30 days after treatment. — Martin Gidron

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