DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

TRANSMITTED BY FACSIMILE

Stacy Holdsworth, PharmD
Manager
U.S. Regulatory Affairs
Eli Lilly and Company
Lilly Technology Center
Indianapolis, IN 46221

RE: NDA 21-411
Strattera (atomoxetine HCl)
MACMIS ID#: 13282

Dear Dr. Holdsworth:

This Division of Drug Marketing, Advertising, and Communications (DDMAC) has reviewed a 60-second direct-to-consumer (DTC) television broadcast advertisement (TV ad) entitled "Videogame" (ID# LLST-5046/AT357083000126131) for Strattera (atomoxetine HCl) Capsules submitted by Eli Lilly and Company (Lilly) under cover of Form FDA 2253. The TV ad is false or misleading because it inadequately communicates the indication for Strattera and minimizes the risks associated with Strattera. Thus, the TV ad misbrands the drug within the meaning of the Federal Food, Drug, and Cosmetic Act (Act) (21 U.S.C. 352(n)) and FDA implementing regulations. 21 CFR 202.1(e)(6)(xviii) and (e)(6)(i). This ad is concerning from a public health perspective because by failing to adequately communicate the Attention-Deficit Disorder (ADD) indication for Strattera, it potentially broadens the use of the drug beyond the indicated patient population, while also minimizing the serious risks associated with the drug.

Background

Strattera is an orally administered psychotropic drug approved for treatment of Attention-Deficit/Hyperactivity Disorder (ADHD). The TV ad in question promotes Strattera for Attention-Deficit Disorder (ADD); the symptoms shown by adults who primarily have attention problems associated with ADHD (i.e., the "Inattentive Type" – see below), but not hyperactivity have been commonly described as ADD. The Indications and Usage section of the FDA-approved labeling (PI) states (in pertinent part):

> A diagnosis of ADHD (DSM-IV) implies the presence of hyperactive-impulsive or inattentive symptoms that cause impairment and that were present before age 7 years. The symptoms must be persistent, must be more severe than is typically observed in individuals at a comparable level of development, must cause clinically significant impairment, e.g., in social, academic, or

occupational functioning, and must be present in 2 or more settings, e.g., school (or work) and at home. The symptoms must not be better accounted for by another mental disorder. For the Inattentive Type, at least 6 of the following symptoms must have persisted for at least 6 months: lack of attention to details/careless mistakes, lack of sustained attention, poor listener, failure to follow through on tasks, poor organization, avoids tasks requiring sustained mental effort, loses things, easily distracted, forgetful….

Special Diagnostic Considerations

The specific etiology of ADHD is unknown, and there is no single diagnostic test. Adequate diagnosis requires the use not only of medical but also of special psychological, educational, and social resources. Learning may or may not be impaired. The diagnosis must be based upon a complete history and evaluation of the patient and not solely on the presence of the required number of DSM-IV characteristics.

Need for Comprehensive Treatment Program
STRATTERA is indicated as an integral part of a total treatment program for ADHD that may include other measures (psychological, educational, social) for patients with this syndrome. Drug treatment may not be indicated for all patients with this syndrome. Drug treatment is not intended for use in the patient who exhibits symptoms secondary to environmental factors and/or other primary psychiatric disorders, including psychosis. Appropriate educational placement is essential in children and adolescents with this diagnosis and psychosocial intervention is often helpful. When remedial measures alone are insufficient, the decision to prescribe drug treatment medication will depend upon the physician's assessment of the chronicity and severity of the patient's symptoms.

Strattera is contraindicated in patients who have narrow angle glaucoma, or patients who have taken medications known as monoamine oxidase inhibitors (MAOIs) in the last two weeks because taking Strattera with an MAOI could cause serious side effects or be life-threatening.

The Warnings section of the PI states, in part:

Severe Liver Injury
Postmarketing reports indicate that STRATTERA can cause severe liver injury in rare cases. Although no evidence of liver injury was detected in clinical trials of about 6000 patients, there have been two reported cases of markedly elevated hepatic enzymes and bilirubin, in the absence of other obvious explanatory factors, out of more than 2 million patients during the first two years of postmarketing experience. In one patient, liver injury, manifested by elevated hepatic enzymes (up to 40 X upper limit of normal (ULN)) and jaundice (bilirubin up to 12 X ULN), recurred upon rechallenge, and was followed by recovery upon drug discontinuation providing evidence that STRATTERA caused the liver injury. Such reactions may occur several months after therapy is started, but laboratory abnormalities may continue to worsen for several weeks after drug is stopped. Because of probable underreporting, it is impossible to provide an accurate estimate of the true incidence of these events. The patients described above recovered from their liver

injury, and did not require a liver transplant. However, in a small percentage of patients, severe drug-related liver injury may progress to acute liver failure resulting in death or the need for a liver transplant.

STRATTERA should be discontinued in patients with jaundice or laboratory evidence of liver injury, and should not be restarted. Laboratory testing to determine liver en enzyme levels should be done upon the first symptom or sign of liver dysfunction (e.g., pruritus, dark urine, jaundice, right upper quadrant tenderness, or unexplained "flu-like" symptoms). (See also Information for Patients under PRECAUTIONS.)

Additionally, the Precautions section of the PI states, in part: "STRATTERA should be used with caution in patients with hypertension, tachycardia, or cardiovascular or cerebrovascular disease because it can increase blood pressure and heart rate."

Furthermore, the Adverse Reactions section of the PI identifies constipation, dry mouth, nausea, decreased appetite, dizziness, insomnia, decreased libido, ejaculatory problems, impotence, urinary hesitation and/or urinary retention and/or difficulty in micturation and dysmenorrheal as side effects observed in some adult patients with ADD.

Misleading Communication of Indication

A prescription drug advertisement is misleading if it uses headline, subheadline, or pictorial or other graphic matter in a way that is misleading, 21 CFR 202.1(e)(6)(xviii). The TV ad presents images and contains statements in voiceover relating to the product's indication. Specifically, the ad visually presents a person in a variety of situations as seen through the screen of a videogame, including: leaving the house; walking to his car; going back to the house for his car keys; looking into a shop; looking at a wristwatch; handing in a "Quarterly Report;" and sitting down at a desktop computer. These scenes are presented with a box in the middle right of the screen that displays a descriptor or attribution for each behavior (e.g., "DISORGANIZED," "DISTRACTED," "TROUBLE FINISHING THINGS") and the word "penalty" beneath it. These descriptors convey information related to the product's indication. Additionally, the ad references the product's indication in the audio (as "If these symptoms have frustrated you your whole life, it could be adult ADD, a condition your doctor can diagnose and treat with prescription Strattera the only non-stimulant treatment for Adult ADD") and in a small SUPER (the lower-left hand corner of the screen flashes and scrolls the words "Adult Attention-Deficit Disorder" one time).

The TV ad fails to clearly communicate the indication for Strattera because of competing visuals, graphics, and music that are presented at the same time as the information described above relating to the indication. As stated above, the images that are presented relating to the product's indication are portrayed as seen through the screen of a videogame. The viewpoint of the screen changes periodically, from seeing the world through the eyes of the actor playing the main character, to seeing the character himself and back again. During the presentation of the various situations the character is engaged in, a box with the words "SCORE" (including a running tally of numbers) and "LEVEL 1" is shown in the upper right-hand corner of the screen and another box with superimposed text is shown in the middle of the right of the screen. The text scrolls and flashes. The text, graphics, and voice-over

are also accompanied by eerie sound effects. All of this distracts from the viewer's ability to process the visual information related to the product's indication. Similarly, at the same time as the audio information and the SUPER defining ADD are presented, there are numerous competing and distracting elements, such as a large SUPER in the middle right of the screen that types out the word "RESTLESS_penalty," a SUPER in the upper right-hand corner with the words "LEVEL 1" and "SCORE" which loses points every time a symptom is displayed in the middle right super, a SUPER in an image of a computer covered in reminder notes, and an image of the actor's hands with his fingers interlacing and stretching. All of these competing graphics distract from and overcome the important contextual information to such an extent the presentation interferes with the viewer's ability to process the information in the ad relating to the indication.

Minimization of Risk

The audio communication of serious risk disclosures in the "major statement" is minimized by the distracting visuals and graphics/SUPERs, which combine to interfere with the presentation of the risk information. The audio presentation of risk information is accompanied by concurrent erratic camera movement, quick scene changes, and visual changes in point-of-view. There are multiple SUPERs presented on the screen during the risk information. The SUPERs scroll in and out and flash, and the "SCORE" in the top right-hand corner of the screen is constantly moving (gaining points). The risk information is presented very rapidly in the audio while important contextual information and other informational elements are presented sequentially in subtitled SUPERs (e.g., "Strattera.com," "Strattera logo," "Individual results may vary," "SUSTAINED ATTENTION_bonus," "Strattera has not been tested in geriatric patients," "see our ad in Health," and a toll-free number). Many of these SUPERs flash when they appear on the screen. The SUPERs are presented in small-light colored type, rendering them extremely difficult to read under normal conditions, and more so where they are presented against moving backgrounds and with overlying music. The overall effect of the distracting visuals and graphics, including competing messages related to efficacy, and the competing audio message is to undermine the consumer's ability to pay attention to and comprehend the risk information, thereby minimizing these risks and misleadingly suggesting that Strattera is safer than has been demonstrated by substantial evidence or substantial clinical experience. See 21 CFR 202.1(e)(6)(i).

Conclusion and Requested Actions

For the reasons discussed above, the TV ad misbrands Strattera under section 502(n) of the Act, 21 U.S.C. § 352(n), and FDA implementing regulations, 21 CFR 202.1(e)(6)(xviii) and (e)(6)(i).

DDMAC requests that Lilly immediately cease the dissemination of promotional materials for Strattera the same as or similar to those described above. Please submit a written response to this letter on or before June 28, 2005 describing your intent to comply with this request, listing all promotional materials for Strattera the same as or similar to those described above, and explaining your plan for discontinuing use of such materials. Please direct your response to me at the Food and Drug Administration, Division of Drug Marketing, Advertising, and Communications, HFD-42, Rm. 8B-45, 5600 Fishers Lane, Rockville, Maryland 20857, facsimile at (301) 594-6771.

In all future correspondence regarding this matter, please refer to MACMIS ID# 13282 in addition to the NDA number. We remind you that only written communications are considered official. The violations discussed in this letter do not necessarily constitute an exhaustive list. It is your responsibility to ensure that your promotional materials for Strattera comply with each applicable requirement of the Act and FDA implementing regulations.

Sincerely,

{See appended electronic signature page}

Joan Hankin, J.D.
Consumer Promotion Analyst
Regulatory Review Officer
Division of Drug Marketing,
Advertising, and Communications

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Joan Hankin
6/14/05 11:39:27 AM