DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

TRANSMITTED BY FACSIMILE

John Lechleiter, Ph.D.
President & Chief Executive Officer
Eli Lilly & Company
Lilly Technology Center
Indianapolis, IN 46221

RE: NDA # 21-411
Strattera® (atomoxetine HCl)
MACMIS ID # 15564

WARNING LETTER

Dear Dr. Lechleiter:

The Division of Drug Marketing, Advertising, and Communications (DDMAC) of the U.S. Food and Drug Administration (FDA) has reviewed a professional sales aid (AT39696) for Strattera® (atomoxetine HCl) (Strattera) submitted by Eli Lilly and Company (Eli Lilly) under cover of Form FDA 2253. This piece is false or misleading because it broadens the indication for and overstates the efficacy of Strattera, omits material facts, and minimizes important risks associated with Strattera. Thus, the promotional material misbrands the drug in violation of the Federal Food, Drug, and Cosmetic Act (Act), 21 U.S.C. 352(a) & 321(n), and FDA's implementing regulations. *Cf.* 21 CFR 201.100(c)(1); 201.128; & 202.1(e)(6)(i). These violations are concerning from a public health perspective because they suggest that Strattera is safer and more effective than has been demonstrated.

Background

According to its FDA-approved product labeling[1], Strattera is indicated for the treatment of Attention-Deficit/Hyperactivity Disorder (ADHD). The Indications and Usage section of the PI also includes information regarding special diagnostic considerations, the need for comprehensive treatment, and information about long-term use.

The PI for Strattera contains a Boxed Warning regarding the risk of suicidal ideation in children and adolescents. Strattera use is contraindicated in patients taking monoamine oxidase inhibitors (MAOI) or within two weeks after discontinuing an MAOI, and in patients with narrow angle glaucoma. The PI for Strattera also includes a bolded warning regarding

[1] The PI submitted with the sales aid and referred to within this letter is version PV 5311 AMP. We note that the PI for Strattera has since been revised to include, among other changes, the statement "Does not worsen tics in patients with ADHD and comorbid Tourette's Disorder."

severe liver injury and a warning regarding allergic events. Additionally, the PI contains precautions regarding effects on blood pressure and heart rate, effects on urine outflow, effects on growth, and aggressive behavior or hostility. The most commonly observed adverse events in children and adolescents (incidence of 5% or greater and at least twice the incidence in placebo patients) were dyspepsia, nausea, vomiting, fatigue, appetite decreased, dizziness, and mood swings. The most commonly observed adverse events in adults (incidence of 5% or greater and at least twice the incidence in placebo patients) were constipation, dry mouth, nausea, appetite decreased, dizziness, insomnia, decreased libido, ejaculatory problems, impotence, urinary hesitation and/or urinary retention and/or difficulty in micturition, and dysmenorrhea.

Broadening of Indication

The sales aid contains numerous presentations about patients with anxiety and patients with comorbid ADHD and anxiety. The sales aid presents two graphs on page 14, which show:

- a statistically significant difference in mean change from baseline between Strattera and placebo on the Clinician-Rated Pediatric Anxiety Rating Scale (PARS).

- a statistically significant difference in mean change from baseline between Strattera and placebo on the Patient-Rated Multidimensional Anxiety Scale for Children (MASC)

In addition, on page 16, underneath the claim, “Not contraindicated in patients with anxiety,” the sales aid presents a graph showing the mean change from baseline, for Strattera and placebo, on the Hamilton Anxiety Rating Scale (HAM-A). 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. Thus, these presentations broaden the indication for Strattera.[2] Indeed, the Warnings section of Strattera’s PI, under the header "Suicidal Ideation," specifically states that anxiety has been reported in patients treated with Strattera, and that there is concern that symptoms such as anxiety may represent precursors to emerging suicidal impulses. While we note the disclaimer “Strattera is not indicated to treat anxiety disorders” is presented at the bottom of pages 14 and 16, 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.

Similarly, on numerous pages of the sales aid, claims related to the use of Strattera in patients with ADHD and comorbid tics or Tourette’s disorder are presented. For example, page 18 presents a graph showing a statistically significant difference between placebo and Strattera (favoring Strattera) in mean change from baseline in overall impairment as rated by the Yale Global Tic Severity Scale (YGTSS). These presentations are misleading because

[2] We note that after this piece was initially disseminated, Lilly submitted a pre-approval supplement (Supplement 024) to FDA regarding the tolerability of Strattera in pediatric and adult patients with ADHD and comorbid anxiety. However, this supplement was not approved at the time of dissemination of the sales aid, nor does it provide for any efficacy data regarding the treatment of anxiety, but rather it provides for the use of of Strattera in patients with ADHD and comorbid anxiety disorder without causing *worsening* of anxiety.

they suggest or imply that Strattera is safe and effective for the treatment of tics or Tourette's disorder, when in fact, Strattera is not indicated for treatment of tics or Tourette's disorder. Thus, these presentations broaden the indication for Strattera.[3] While we note the disclaimer "Strattera is not indicated to treat tics or Tourette's disorder" is presented at the bottom of page 18, this disclaimer is insufficient to mitigate the overwhelmingly misleading impression that Strattera has been proven effective for the treatment of tics or Tourette's disorder.

Overstatement of Efficacy

On numerous pages of the sales aid, outcome claims related to patients with and without ADHD are presented. Page three of the sales aid presents a graph comparing teens/young adults with ADHD and without ADHD in the following three measurements: sexual partners (19 vs. 7), percentage of subjects who conceived a pregnancy (38% vs. 4%), and percentage of subjects who contracted a sexually transmitted disease (STD) (17% vs. 4%). Additionally, page four presents a graph comparing individuals with ADHD and without ADHD in three measurements: percentage of subjects who have been fired (53% vs. 31%); divorced or separated (28% vs. 15%); and in accidents that totaled a vehicle (49% vs. 16%). Additional outcome claims include the following (emphasis original):

Page 5**:**

> **"Symptoms may lead to negative health outcomes"**
>
> - "Distractibility may lead to car accidents and injuries" (footnote omitted)
> - "Impulsive sexual behavior may lead to teen pregnancy, STDs" (footnote omitted)

Page 6:

> **"75% of adolescents with ADHD have a substance abuse disorder"** (footnote omitted)
> "*75% for non-medicated ADHD patients and 25% for medicated ADHD patients, 18% for patients without ADHD." (presented as a footnote to the above claim)

While these presentations do not directly assert that Strattera will correct the negative outcomes associated with ADHD, the implication created by placing these presentations in a piece promoting Strattera for treatment of ADHD is that treating ADHD patients with Strattera will reduce the likelihood or severity of the negative outcomes associated with ADHD. Thus, 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. While Strattera has been shown to improve total scores on the ADHD-RS-IV-

[3] We note that after this piece was initially disseminated, Lilly submitted to FDA a pre-approval supplement (NDA 21-411 Supplement 019) regarding the tolerability of Strattera in pediatric and adult patients with ADHD and comorbid tics and Tourette's disorder. However, this supplement was not approved at the time of dissemination of the sales aid, nor does it provide for any efficacy data regarding the treatment of tics or Tourette's disorder.

Parent: INV[4], which measures ADHD symptoms such as fidgeting, not listening, and talking excessively, this scale does not measure the impact of treatment on the outcomes listed above (i.e., impulsive sexual behavior, poor job success, marital problems, contraction of sexually transmitted diseases, motor vehicle accidents, and substance abuse disorder), and it does not necessarily follow that improvement in ADHD-RS-IV-Parent:INV total scores correlates with a positive effect on the outcomes listed in the piece.

Furthermore, numerous pages of the sales aid present claims regarding improvement of Strattera efficacy over time. These claims are misleading because they suggest that Strattera has been shown to be increasingly effective in reducing ADHD symptoms the longer it is used by a patient when this has not been demonstrated by substantial evidence or substantial clinical experience. For example, on page 22, the claim "Efficacy builds over time for children" is presented in conjunction with a graph illustrating mean ADHD-Rating Scale (ADHD-RS) scores over seven weeks of treatment as reported by teachers during school. Similarly, on page 23, the claim "Efficacy builds over time for adults" is presented in conjunction with a graph illustrating "CAARS-Inv:SV Total ADHD Symptom Score LS Means"[5] over ten weeks of treatment as reported by investigators in two separate trials. In both graphs, children and adults treated with Strattera show a steady decrease over time in mean ADHD scores as rated by their respective rating scales. However, the cited studies do not support the claims that "Efficacy builds over time" because they do not show any additional improvement over placebo once overall efficacy has been achieved. We are not aware of substantial evidence or substantial clinical experience that supports the claims made in the piece that Strattera becomes increasingly effective the longer it is used. Therefore, these presentations and similar presentations are misleading.

Omission of Material Fact

Promotional materials are misleading if they fail to reveal facts that are material in light of the representations made or with respect to consequences that may result from the use of the drug as recommended or suggested in the materials. The sales aid presents numerous claims regarding the effect of Strattera on time to sleep onset compared with methylphenidate. Specifically, page 30 of the sales aid claims, "Children with ADHD taking Strattera fall asleep faster than children with ADHD taking methylphenidate." Below the claim, two graphs show a statistically significant difference in mean change from baseline in time to sleep onset between Strattera and methylphenidate as measured by actigraphy and polysomnography. Additionally, on page 31, the sales aid claims "In the sleep study, there was no difference in efficacy between children on Strattera and children on methylphenidate; there was no correlation between ADHD symptom response and sleep onset." Below the claim, a graph showing mean change from baseline to endpoint in ADHD-RS total score for Strattera and methylphenidate is presented. These presentations are misleading because they fail to include material facts regarding the risk of insomnia associated with Strattera use. Specifically, as reflected in the Adverse Reactions section of the Strattera PI, insomnia has been associated with Strattera use in both child and adolescent clinical trials and adult clinical trials. Additionally, Strattera's Medication Guide states that parents should watch for and

[4] Attention Deficit Hyperactivity Disorder Rating Scale-IV Parent Version: Investigator Administered and Scored
[5] Connors' Adult ADHD Rating Scale-Investigator Rated: Screening Version Total ADHD Symptom Score Least-Squares Means

contact their child's healthcare provider right away if their child exhibits "[d]ifficulty sleeping (insomnia)."

Minimization of Risk

Page 24 of the sales aid claims that with respect to both adults and children treated with Strattera, “GI upset and somnolence are commonly transient upon starting treatment.” This claim is misleading because it minimizes the risks associated with use of Strattera. According to the PI, the most common treatment-emergent adverse events associated with the use of Strattera in acute (up to 9 weeks) child and adolescent trials include (with percentage of patients) upper abdominal pain (20%), constipation (3%), dyspepsia (4%), vomiting (11%), and somnolence (7%). Additionally, common treatment-emergent adverse events associated with the use of Strattera in acute (up to 10 weeks) adult trials include (with percentage of patients) constipation (10%), dry mouth (21%), dyspepsia (6%), flatulence (2%), and nausea (12%). FDA is not aware of any data supporting the claim that these adverse events are transient in nature. If you have such data, please submit them to FDA for review.

Furthermore, Page 36 of the sales aid presents a chart of the most common side effects in child and adolescent trials of Strattera. Page 37 presents a chart of the most common side effects in adult trials of Strattera. Both charts report the incidence of side effects relative to placebo and include either a p-value or a designation of “NS,” meaning not significant. This presentation is misleading because it implies that those adverse events designated as non-significant compared with placebo are not attributable to an adverse effect of Strattera. In fact, the studies were not powered to detect whether these differences exist and therefore, the designation of adverse events rates as “NS” misleadingly minimizes the risks of these adverse reactions.

Conclusion and Requested Action

For the reasons discussed above, the promotional piece misbrands Strattera in violation of the Federal Food, Drug, and Cosmetic Act (Act), 21 U.S.C. 352(a) & 321(n), and FDA’s implementing regulations. *Cf.* 21 CFR 201.100(c)(1); 201.128; & 21 CFR 202.1(e)(6)(i).

DDMAC requests that Lilly immediately cease the dissemination of violative promotional materials for Strattera such as those described above. Please submit a written response to this letter on or before October 7, 2008, stating whether you intend to comply with this request, listing all violative promotional materials for Strattera the same as or similar to those described above, and explaining your plan for discontinuing use of such materials. Because the violations described above are serious, we request, further, that your submission include a comprehensive plan of action to disseminate truthful, non-misleading, and complete corrective messages about the issues discussed in this letter to the audience(s) that received the violative promotional materials. Please direct your response to me at the Food and Drug Administration, Center for Drug Evaluation and Research, Division of Drug Marketing, Advertising, and Communications, 5901-B Ammendale Road, Beltsville, MD 20705-1266, or facsimile at 301-847-8444. In all future correspondence regarding this matter, please refer to MACMIS # 15564 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.

Failure to correct the violations discussed above may result in FDA regulatory action, including seizure or injunction, without further notice.

Sincerely,

{See appended electronic signature page}

Thomas Abrams, R.Ph.,M.B.A.
Director
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/

Thomas Abrams

9/25/2008 04:17:52 PM