

**TRANSMITTED BY FACSIMILE**

Angus Russell
Chief Executive Officer
Shire Development Inc.
725 Chesterbrook Blvd.
Wayne, PA 19087-5637

RE: NDA # 21-303
Adderall XR[®] Capsules
MACMIS # 15563

WARNING LETTER

Dear Mr. Russell:

The Division of Drug Marketing, Advertising, and Communications (DDMAC) of the U.S. Food and Drug Administration (FDA) has reviewed a webpage¹ and a video testimonial featuring Ty Pennington² posted on youtube.com by Shire Development Inc. (Shire) for Adderall XR[®] Capsules (Adderall XR). Both the webpage and video overstate the efficacy of Adderall XR; the video also omits important information regarding the risks associated with Adderall XR use. Additionally, the webpage broadens the indication for Adderall XR by suggesting uses that have not been approved by FDA. Thus, the webpage and video misbrand the drug in violation of the Federal Food, Drug, and Cosmetic Act (Act), 21 U.S.C. 352(a), 352(n) & 321(n). Cf. 21 CFR 201.100; 201.128; 202.1(e)(5) & (e)(6)(i). In addition, the video posted on youtube.com was not submitted to FDA under cover of Form 2253, as required by 21 CFR 314.81(b)(3)(i). The webpage and video raise significant public health and safety concerns through their overstatement of efficacy and omission of important safety information.

Background

According to its FDA-approved product labeling (PI), Adderall XR 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.

Adderall XR has numerous contraindications, including use in patients with advanced arteriosclerosis, symptomatic cardiovascular disease, moderate to severe hypertension, hyperthyroidism, known hypersensitivity to sympathomimetic amines, glaucoma, patients in

¹ Available at http://www.adderallxr.com/adolescence_adhd/consequences/index.asp. Last accessed September 25, 2008.

² Previously available on YouTube at <http://www.youtube.com/watch?v=BO6BOF00aKY>. Shire acknowledged its involvement in the development and dissemination of the video. A version of this video also appeared on the Adderall XR webpage.

agitated states, patients with a history of drug abuse, and use during or within 14 days following the administration of monoamine oxidase inhibitors. Adderall XR is associated with a number of serious risks, some of which may be fatal. These risks include serious cardiovascular events, hypertension, psychiatric events, aggression, long-term suppression of growth, seizures, and visual disturbances. Additionally, the PI for Adderall XR contains a general precaution regarding overdosage as well as precautions for patients with tics and Tourette's syndrome. Furthermore, the Adverse Events section of the PI states that Adderall XR is associated with loss of appetite, insomnia, abdominal pain, and weight loss.

Overstatement of Efficacy/Broadening of Indication - Webpage

The webpage entitled "**Difficulties caused by ADHD in adolescence**" presents numerous claims about the consequences of untreated ADHD and claims about the impact of treatment with Adderall XR, including the following (citations omitted):

ADHD in adolescents

ADHD may have an effect on all aspects of a teen's life. In addition to causing academic problems for teens, ADHD may lead to difficulty maintaining friendships, focusing on sports or other after-school activities, and relating with family members. Over the long term, untreated ADHD may have a lasting, negative impact on job success and social-emotional development.

In fact, studies suggest that untreated ADHD may have some very serious consequences including the following:

Schooling

- Up to 58% of children with ADHD have failed a grade
- As many as 30% of teens with ADHD drop out of or don't complete high school, compared with 10% of non-ADHD teens

Impulsive behavior

- As many as 40% 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

Sexual health

- 17% of young adults with ADHD are likely to have contracted a sexually transmitted disease (STD), compared with 4% of those without ADHD
- 38% of young adults with ADHD are likely to have been pregnant or caused a pregnancy, compared with 4% of those without the condition

Injury rates

- Adolescents who did not take their ADHD medication regularly had:
 - Four times as many serious injuries
 - Three times as many motor vehicle accidents

However, ADHD may be successfully treated. Today's ADHD medications, like ADDERALL XR, have come a long way in providing better symptom control.

This presentation is misleading because it implies that Adderall XR reduces the likelihood or severity of the "difficulties" and "consequences" of "untreated ADHD" listed above (i.e., poor social-emotional development and job success, inability to complete schooling, illegal behaviors, contraction of sexually transmitted diseases, motor vehicle accidents, and physical injury), when this has not been demonstrated by substantial evidence or substantial clinical experience. While Adderall XR has been shown to improve total scores on the Attention Deficit Hyperactivity Disorder Rating Scale-IV (ADHD-RS-IV), 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 academic performance, contraction of sexually transmitted diseases, and motor vehicle accidents), and it does not necessarily follow that improvement in ADHD-RS-IV total scores is correlated with a positive effect on these outcomes.

None of the references cited^{3, 4, 5} in support of the claims presents data on the effect of treatment with Adderall XR on the outcomes presented on the webpage. The National Institute of Mental Health 2003 publication about ADHD³ provides an overview of ADHD and its management but presents no data on the efficacy or safety of Adderall XR. Barkley et al.⁴ studied academic and social outcomes in young adults diagnosed with ADHD but did not study the effects of drug treatment on those outcomes. Spencer et al.⁵ evaluated symptom improvement in adolescents with ADHD treated with Adderall XR but did not study the effect of Adderall XR on treatment outcomes such as the consequences of behavior listed above. If you have data to support these claims, please submit them to FDA for review.

Furthermore, the presentation on the webpage under the "Impulsive behavior" heading (see above) 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. This presentation thereby broadens the indication for Adderall XR.

³ National Institute of Mental Health. Attention Deficit Hyperactivity Disorder. Bethesda (MD): National Institute of Mental Health, National Institutes of Health, US Department of Health and Human Services; 2003. NIH Publication Number: NIH 3572.

⁴ Barkley RA, Fischer M, Smallish L, et al. Young adult outcomes of hyperactive children: adaptive functioning in major life activities. *J Am Acad Child Adolesc Psychiatry*. 2006;45(2):192-202.

⁵ Spencer T, Wilens T, Biederman J, et al. Efficacy and safety of mixed amphetamine salts extended release (Adderall XR) in the management of attention deficit/hyperactivity disorder in adolescent patients: a 4-week, randomized, double-blind, placebo-controlled, parallel-group study. *Clin Therapeutics*. 2006;266-279.

Overstatement of Efficacy - Video

The video consists of the testimonial of a celebrity, Ty Pennington, promoting the use of Adderall XR with claims that include the following (emphasis added):

Now once I got on medication it's just **amazing** the **transformation** I made. I -- It **literally changed my life**, and **gave me the confidence to achieve my goals**, like being an artist. As a kid, I never could have imagined I could do it. But with the medicines like **Adderall XR, it's truly a transformation**. I mean talk about an Extreme Makeover, I'm like living it. Now growing up with ADHD can be a little difficult. It's **not easy to communicate with people**, including your own family. So you become kind of **alienated**. You **feel like you're different, and you don't really fit in**. And that, well, can kind of cause you to feel different, and nobody likes to feel different. So as someone who has had ADHD, and is overcoming it, **proper treatment has truly changed my life and made an amazing difference**.

This video overstates the efficacy of Adderall XR by implying that this product will “transform” patients’ lives and improve their “confidence.” These claims imply an impact on aspects of a patient’s life that are much broader than those actually impacted by Adderall XR treatment. 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.” FDA is not aware of substantial evidence or substantial clinical experience demonstrating that treatment with Adderall XR has a beneficial effect on these behaviors and feelings, which are not core symptoms of ADHD. The video cites no references in support of these claims, and we are not aware of substantial evidence to support them. In fact, the effect of Adderall XR on patients’ total scores on the ADHD-RS-IV in clinical trials versus placebo, while statistically significant, does not demonstrate an effect that in any way supports the “amazing transformation” claim, nor do the symptoms measured in this rating scale include the outcomes claimed in this testimonial (i.e., fitting in, effectively communicating, not feeling different). If you have data to support these claims, please submit them to FDA for review.

Omission of Risk Information

Promotional materials are misleading if they fail to reveal facts that are material in light of representations made by the materials or with respect to consequences that may result from the use of the drug as recommended or suggested by the materials. The video presents numerous efficacy claims for Adderall XR (see above), but entirely omits risk information for Adderall XR, including the contraindications, warnings, precautions, and common adverse events associated with the drug.

Failure to Submit Under Form 2253

FDA regulations require sponsors to submit specimens of mailing pieces and any other labeling or advertising devised for promotion of the drug product at the time of initial dissemination of the labeling and at the time of initial publication of the advertisement for a

prescription drug product. Each submission is required to be accompanied by a completed transmittal Form FDA-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) and is required to include a copy of the product's current professional labeling. See 21 CFR 314.81(b)(3)(i).

You did not submit the video to FDA under cover of Form 2253 as required by 21 CFR 314.81(b)(3)(i).

Conclusion and Requested Action

For the reasons discussed above, the promotional pieces misbrand Adderall XR in violation of the Federal Food, Drug, and Cosmetic Act (Act), 21 U.S.C. 352(a), 352(n) & 321(n). Cf. 21 CFR 201.100(c)(1); 201.128; 202.1(e)(5) & (e)(6)(i). In addition, the video was not submitted to FDA under cover of Form FDA-2253, as required by 21 CFR 314.81(b)(3)(i).

DDMAC requests that Shire immediately cease the dissemination of violative promotional materials for Adderall XR 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 Adderall XR 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 301-847-4444. In all future correspondence regarding this matter, please refer to MACMIS # 15563 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 Adderall XR 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

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