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Shire

James Paicopolos

January 22, 2014

Ref: US14-000376

Subject: Adderall XR® (mixed salts of a single-entity amphetamine product)

Dear James Paicopolos:

Thank you for your recent medical information inquiry regarding Adderall XR®. We understand that you have requested information on neuro-toxic effects of Adderall XR.

ADDERALL XR® PRODUCT SUMMARY

Adderall XR® (mixed salts of a single-entity amphetamine product) is indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in patients ages 6 and above as an integral part of a total treatment program that may include other measures (psychological, educational and social).

The efficacy of Adderall XR in the treatment of ADHD was established on the basis of two controlled trials in children aged 6 to 12, one controlled trial in adolescents aged 13 to 17, and one controlled trial in adults who met DSM-IV® criteria for ADHD. The effectiveness of Adderall XR for more than 3 weeks in children and 4 weeks in adolescents and adults has not been systematically evaluated in controlled trials. Extended use should be periodically reevaluated for long-term usefulness for the individual patient.

WARNING: POTENTIAL FOR ABUSE

Amphetamines have a high potential for abuse. Administration of amphetamines for prolonged periods of time may lead to drug dependence. Pay particular attention to the possibility of subjects obtaining amphetamines for non-therapeutic use or distribution to others and the drugs should be prescribed or dispensed sparingly.

Misuse of amphetamine may cause sudden death and serious cardiovascular adverse reactions.

Adderall XR is contraindicated in patients with advanced arteriosclerosis, symptomatic cardiovascular disease, moderate to severe hypertension, hyperthyroidism, known

hypersensitivity or idiosyncrasy to sympathomimetic amines, glaucoma, agitated states, history of drug abuse, or during or within 14 days after treatment with monoamine oxidase inhibitors (MAOIs) as hypertensive crisis can occur.

Sudden death in children and adolescents with structural cardiac abnormalities or other serious heart problems, as well as sudden death, stroke, and myocardial infarction in adults has been reported in CNS stimulant treatment at usual doses. Stimulants generally should not be used in patients with known structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities, or other serious cardiac problems. Adults have a greater likelihood than children of having such cardiac disease. Patients being considered for stimulant treatment should have a careful history (including assessment for a family history of sudden death or ventricular arrhythmia) and a physical exam to assess for the presence of cardiac disease. Further evaluation should be conducted if needed (e.g., electrocardiogram and echocardiogram). Patients who develop symptoms suggestive of cardiac disease (e.g., exertional chest pain, unexplained syncope) during stimulant treatment should undergo a prompt cardiac evaluation.

Use with caution in patients whose underlying medical condition might be compromised by increases in blood pressure or heart rate. Stimulants cause modest increases in average blood pressure (about 2-4 mmHg) and average heart rate (about 3-6 bpm) and patients may have larger increases. Monitor all patients for larger changes. Use of stimulants may cause psychotic or manic symptoms in patients with no prior history, or exacerbation of symptoms in patients with pre-existing psychosis. Prior to initiating treatment with a stimulant, patients with comorbid depressive symptoms should be adequately screened to determine if they are at risk for bipolar disorder. Monitor for aggressive behavior.

Monitor growth in children during treatment with Adderall XR. Children who are not growing or gaining weight as expected may need to have their treatment interrupted.

Stimulants may lower the convulsive threshold. Discontinue if seizures develop.

Stimulants, including Adderall XR, used to treat ADHD are associated with peripheral vasculopathy, including Raynaud® phenomenon. Signs and symptoms generally improve after reduction in dose or discontinuation of drug. Careful observation for digital changes (e.g., numbness, pain, skin color change, or sensitivity to temperature and rarely ulcerations and/or soft tissue breakdown) is necessary during treatment and may require further evaluation (e.g. referral).

Visual disturbances and exacerbation of tics and Tourette's syndrome have been reported with stimulant treatment.

The most common adverse reactions (>_ 5% and with a higher incidence than on placebo) reported with Adderall XR during the clinical trials were:

- Children ages 6-12: loss of appetite, insomnia, abdominal pain, emotional liability, vomiting, nervousness, nausea, and fever;
- Adolescents ages 13-17: loss of appetite, insomnia, abdominal pain, weight loss, and nervousness;

- Adults: dry mouth, loss of appetite, insomnia, headache, weight loss, nausea, anxiety, agitation, dizziness, tachycardia, diarrhea, asthenia, and urinary tract infections.

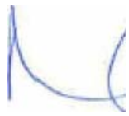
Adderall XR is available as 5 mg, 10 mg, 15 mg, 20 mg, 25 mg and 30 mg extended release capsules. Dosage of Adderall XR should be individualized according to the therapeutic needs and response of the patient and administered at the lowest effective dosage. Please refer to Adderall XR prescribing information for specific dosing information.

The above product summary does not include all of the information needed to use Adderall XR safely and effectively. Please see the enclosed Full Prescribing Information, including the Boxed Warning regarding Potential for Abuse for Adderall XR.

This information is supplied as a courtesy in response to your inquiry. It is not intended to recommend any indication, dosage, or other use that is not covered in the Adderall XR® package insert(s).

Please discuss this information and any additional questions with your physician or health care provider. He or she knows your medical history and is in the best position to give you appropriate information about your medications.

Sincerely,



Noemie Berube-Carriere, PhD
Medical Affairs Associate

Enclosure:
Adderall XR [Package Insert]. Wayne, PA: Shire US Inc.

Neuro-toxic Effects of Adderall XR

Thank you for your enquiry regarding animal or human study data on neuro-toxic effects, memory loss, effects on IQ, and brain atrophy associated with the use of Adderall XR® (mixed salts of a single-entity amphetamine product). Please see relevant Prescribing Information below pertaining to these topics. A copy of the prescribing information is enclosed.

Please discuss this information and any additional questions with your physician or health care provider. He or she knows your medical history and is in the best position to give you appropriate information about your medications.

RELEVANT PRESCRIBING INFORMATION

NONCLINICAL TOXICOLOGY Animal

Toxicology and/or Pharmacology

Acute administration of high doses of amphetamine (d- or d,l-) has been shown to produce long-lasting neurotoxic effects, including irreversible nerve fiber damage, in rodents. The significance of these findings to humans is unknown (Adderall XR PI).

USE IN SPECIFIC POPULATIONS

Pediatric Use

In a juvenile developmental study, rats received daily oral doses of amphetamine (d to l enantiomer ratio of 3:1, the same as in Adderall XR) of 2, 6, or 20 mg/kg on days 7-13 of age; from day 14 to approximately day 60 of age these doses were given b.i.d. for total daily doses of 4, 12, or 40 mg/kg. The latter doses are approximately 0.6, 2, and 6 times the maximum recommended human dose for children of 30 mg/day, on a mg/m2 basis. Post dosing hyperactivity was seen at all doses; motor activity measured prior to the daily dose was decreased during the dosing period but the decreased motor activity was largely absent after an 18 day drug-free recovery period. Performance in the Morris water maze test for learning and memory was impaired at the 40 mg/kg dose, and sporadically at the lower doses, when measured prior to the daily dose during the treatment period; no recovery was seen after a 19 day drug-free period. A delay in the developmental milestones of vaginal opening and preputial separation was seen at 40 mg/kg but there was no effect on fertility (Adderall XR PI).

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References

ADDERALL XR® [package insert]. Wayne, PA: Shire US Inc.