CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

021303Orig1s005

Trade Name:	ADDERALL XR
Generic or Proper Name:	Dextroamphetamine Saccharate , Amphetamine Aspartate Monohydrate Dextroamphetamine Sulfate Amphetamine Sulfate
Sponsor:	Shire
Approval Date:	08/11/2004
Indication:	ADDERALL XR™ is indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD).

CENTER FOR DRUG EVALUATION AND RESEARCH

021303Orig1s005

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

021303Orig1s005

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-303/S-005

Shire Laboratories, Inc.
Attention: Stephen W. Sherman, JD
Senior Director, Regulatory Affairs
U.S. Research and Development
1801 Research Blvd., Suite 600
Rockville, MD 20850

Dear Mr. Sherman:

Please refer to your supplemental new drug application dated December 18, 2002, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Adderall XR (mixed salts of a single-entity amphetamine product) Extended-Release Capsules.

We acknowledge receipt of your additional submissions dated:

May 8, 2003	August 12, 2003	September 2, 2003	February 27, 2004
July 11, 2003	August 22, 2003	October 27, 2003	July 14, 2004
August 6, 2003	August 26, 2003	February 13, 2004	

Your submission of February 13, 2004 constituted a complete response to our October 17, 2003 action letter.

This supplemental new drug application provides for the use of Adderall XR in the treatment of adult attention deficient hyperactivity disorder (ADHD). (b) (4)----------
(b) (4)----------

We have completed our review of this application, as amended. This application is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert).

Please submit the FPL electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format – NDA. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved supplement NDA 21-303/S-005." Approval of this submission by FDA is not required before the labeling is used.

In addition, you must submit the content of labeling in electronic format as described in 21 CFR 314.50(l)(5). Current guidance for industry specifies that the content of labeling should be provided in PDF file format. This new submission requirement was published on December 11, 2003 (68 FR

69009) and was effective June 8, 2004. For additional information, consult the following guidance for industry: *Regulatory Submissions in Electronic Format – Content of Labeling* (February 2004).

Pediatric Research Equity Act (PREA)
All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We are waiving the pediatric study requirement for ages less than 6 years and deferring pediatric studies for ages 13 to 17 years for this application.

Your deferred pediatric studies required under section 2 of the Pediatric Research Equity Act (PREA) are considered required postmarketing study commitments. The status of these postmarketing studies shall be reported annually according to 21 CFR 314.81. These commitments are listed below.

LIST POSTMARKETING COMMITMENTS:
1. Deferred pediatric study under PREA for the treatment of ADHD in pediatric patients ages 13 to 17.

   Final Report Submission: May 2008

Submit final study reports to this NDA. For administrative purposes, all submissions related to this/these pediatric postmarketing study commitments must be clearly designated "**Required Pediatric Study Commitments**".

Promotional Materials
In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to this division/ the Division of Neuropharmacological Drug Products and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Medwatch
If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HFD-410
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Richardae Taylor, Pharm.D., Regulatory Project Manager, at (301) 594-5793.

Sincerely,

{See appended electronic signature page}
Russell Katz, M.D.
Director
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure

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

/s/

Russell Katz
8/11/04 10:58:28 AM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

021303Orig1s005

OTHER ACTION LETTERS

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-303/S-005 & [redacted]

Shire Pharmaceutical Development, Inc.
Attention: Rick Lilley, Ph.D.
Senior Vice President, Regulatory Affairs
U.S. Research & Development
1801 Research Blvd., Suite 600
Rockville, MD 20850

Dear Mr. Lilley:

Please refer to your supplemental new drug applications dated December 18, 2002, and June 20, 2003, S-005 [redacted], respectively, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for ADDERALL XR® Extended-release Capsules.

We acknowledge receipt of your amendments dated May 8, July 11, August 6 and 8, 2003 (S-005) and June 20 and July 35, 2003 [redacted]

These supplemental new drug applications provide for the treatment of attention deficit hyperactivity disorder (ADHD) in adult [redacted]

We have completed the review of these applications, as submitted with the draft labeling, and they are approvable. Before these applications may be approved, however, it will be necessary for you to address the following:

Clinical Deficiencies

1. Our review of Study 303 suggests that efficacy does not increase with doses greater than 20 mg/day. Though doses of 40 and 60 mg separated from placebo and were effective in the treatment of ADHD, and there appears to be a numerical increase in the estimate of the treatment effect with increasing dose, our analyses suggest that there is no linear dose trend. We acknowledge that there did not seem to be a dose response for reported adverse events in Study 303; however, we have been unable to find analyses of patients who met outlier criteria for vital sign changes by dose. We ask you to provide these analyses. [redacted]

2. We were unable to find any analyses of ECG abnormalities and changes from baseline to endpoint by dose group in Study 303. Please provide this along with a summary of your findings. In addition, we note that you have detected a slight increase in the mean QTc interval in patients treated with Adderall XR compared to placebo in Study 303. However, we have not been able to determine the method of correction you used to calculate the QTc interval. Please present the method you performed and the rationale for this particular choice.

3. We were not able to clearly establish the extent of exposure of Adderall XR in the studies in the adult population. Your Table 4, Extent of Exposure in Multiple Dose Studies, implies that only 60 patients received Adderall XR for 6-months or greater at any dose and that only 19 patients received 60-mg for a period of 6-months or greater. Please confirm whether or not this is correct. Based on discussions with you, we had anticipated that you would present data on a much larger group of adults (about 200 patients treated for at least 6 months). If we are correct in our calculations of the number of patients who received treatment for 6 months or longer, you will need to accrue considerably more long-term, prospective, well-monitored safety experience prior to approval.

4. As part of the review of the NDA supplement, the FDA's Adverse Event Reporting System was searched for adverse events reported in association with Adderall products. Among these adverse events were a number of serious events including myocardial infarctions, cerebrovascular accidents, sudden deaths, and non-fatal cardiac arrhythmias. Of particular concern to us is the fact that a number of these events occurred in relatively young adults who appeared to have no other explanation for their event. While it is not possible to assign drug causality in individual cases, one way to assess potential safety signals is to calculate reporting rates for each of the adverse events of interest and compare them to the pertinent background rates. We request that you calculate reporting rates (number of cases/person-time exposure) for the following adverse events and compare these rates to the pertinent background rates.

    - Sudden death
    - Myocardial infarction
    - Cerebrovascular accidents/transient ischemic attacks
    - Non-fatal ventricular arrhythmia
    - Cardiomyopathy
    - Seizure
    - Ischemic organ damage

5. Because many of the events are occurring in a relatively young population (20's-40's), it is crucial that the reporting rates be stratified into the pertinent age strata. The reporting rates should then be compared to background rates that are stratified by age. Background rates for these events may be available in the medical literature. Alternatively, there may be some events for which a background rate may be estimated from a data source such as the National Hospital Discharge Survey.

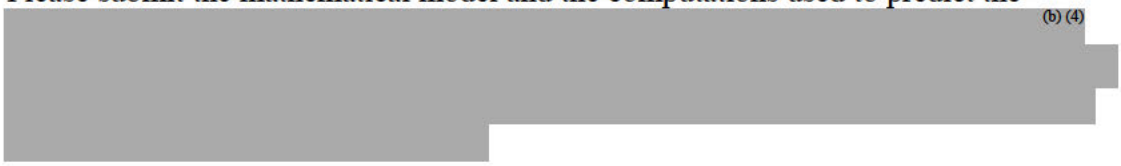
In support of your assessment, please provide the individual MedWatch reports for the cases included in your calculations and also for cases not included in your calculations because of obvious confounding. It should be made clear which cases were included and which were excluded from the calculations. Additionally, please provide your method for calculating the person-time exposure. All relevant published literature related to the observed adverse events should also be reviewed and summarized.

6. We are concerned that there may be deficiencies in the reporting and tabulation of adverse events presented in the application. These deficiencies can be considered to fall into several categories. For example, we detected cases in which: 1) a number of narrative summaries did not include what appear to have been important adverse events (e.g., Patient 106-009 developed muscle cramps, which appeared to have been the primary reason for discontinuation; this event was not included in the narrative), 2) questionable judgment was used (e.g., Subject 124-011 withdrew from Study 303 because of a blood pressure of 152/104, which the narrative called "not clinically significant"; this patient also had an unreported 9 lb weight gain, and entered Study 304 despite meeting the exclusion criteria for elevated blood pressure), 3) potential discrepancies in the counting of adverse events occurred (e.g., in the Safety Update, only one serious adverse event, a case of depression, was considered drug related, but Table 16, a table of patients who discontinued study drug in Study 304, shows seven patients who discontinued because of depression); 4) other problems occurred (e.g., Subject 115-012 had a history of a motor vehicle accident [MVA] and was admitted to the hospital because of severe headaches and left arm weakness on treatment; her weakness was attributed to her MVA, but review of her previous records revealed that her MVA had not resulted in any weakness).

   These and other examples raise concerns about the reliability of the presentation of the safety data. In particular, we are concerned that the incidences of specific adverse events presented in summary tables may not accurately reflect the true incidence of some of these events. Please confirm that all reported and recorded treatment emergent adverse events are included in your data presentations.

<u>Biopharmaceutics Issues</u>

1. 

2. Please submit the mathematical model and the computations used to predict the 

3. [redacted] (b) (4)

4. Please adopt the following method and specification for all strengths of Adderall XR:
   Apparatus: USP Apparatus II (paddle)
   Speed of Rotation: 50 rpm
   Media: Stage 1: pH 1.1 dilute HCL for 2 hours (750 mL) at 37 ± 0.5oC
   Stage 2: pH 6.0 Phosphate buffer for 1 hour (950 mL) at 37 ± 0.5oC
   Specifications: In 2 hours, [redacted] (b) (4)
   In 3 hours, [redacted] (b) (4)

Labeling

Accompanying this letter as an attachment is our proposal for the labeling for Adderall XR® Capsules for the adult attention deficit disorder (ADHD) indication. However, this should be considered a very preliminary draft since we anticipate extensive changes based on the results of the analyses we have requested above. Please submit revised draft labeling in accordance with the enclosed labeling (text for the package insert).

Safety Update

Under 21 CFR 314.50(d)(vi)(b), we request that you provide a final safety update for Adderall XR® for the adult ADHD indication.

Regulatory Status Update

Please provide any new information on the worldwide regulatory status of Adderall XR® for the adult ADHD indication, including the status of all actions either taken or pending before foreign regulatory authorities.

World Literature Update

Prior to approval, we will require an updated report on the world archival literature pertaining to the safety of this product for this indication.

In addition, all previous revisions as reflected in the most recently approved labeling must be included. To facilitate review of your submission, please provide a highlighted or marked-up copy that shows the changes that are being made.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

Within 10 days after the date of this letter, you are required to amend the supplemental application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Under 21 CFR 314.102(d) of the new drug regulations, you may request an informal meeting or telephone conference with this division to discuss what further steps need to be taken before the application may be approved.

This product may be considered to be misbranded under the Federal Food, Drug, and Cosmetic Act if it is marketed with these changes prior to approval of this supplemental application.

If you should have any questions, please call Ms. Richardae Taylor, Pharm D, Regulatory Management Officer, at (301) 594-5793.

Sincerely,

{See appended electronic signature page}

Russell Katz, M.D.
Director
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Attachment

11 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page.

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

/s/

Russell Katz

10/17/03 01:39:30 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

021303Orig1s005

LABELING

ADDERALL XR CAPSULES **CII Rx Only**

AMPHETAMINES HAVE A HIGH POTENTIAL FOR ABUSE. ADMINISTRATION OF AMPHETAMINES FOR PROLONGED PERIODS OF TIME MAY LEAD TO DRUG DEPENDENCE. PARTICULAR ATTENTION SHOULD BE PAID 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 EVENTS.

DESCRIPTION

ADDERALL XR™ is a once daily extended-release, single-entity amphetamine product. ADDERALL XR™ combines the neutral sulfate salts of dextroamphetamine and amphetamine, with the dextro isomer of amphetamine saccharate and d,l-amphetamine aspartate monohydrate. The ADDERALL XR™ capsule contains two types of drug-containing beads designed to give a double-pulsed delivery of amphetamines, which prolongs the release of amphetamine from ADDERALL XR™ compared to the conventional ADDERALL® (immediate-release) tablet formulation.

EACH CAPSULE CONTAINS:	5 mg	10 mg	15 mg	20 mg	25 mg	30 mg
Dextroamphetamine Saccharate	1.25 mg	2.5 mg	3.75 mg	5.0 mg	6.25 mg	7.5 mg
Amphetamine Aspartate Monohydrate	1.25 mg	2.5 mg	3.75 mg	5.0 mg	6.25 mg	7.5 mg
Dextroamphetamine Sulfate USP	1.25 mg	2.5 mg	3.75 mg	5.0 mg	6.25 mg	7.5 mg
Amphetamine Sulfate USP	1.25 mg	2.5 mg	3.75 mg	5.0 mg	6.25 mg	7.5 mg
Total amphetamine base equivalence	3.1 mg	6.3 mg	9.4 mg	12.5 mg	15.6 mg	18.8 mg

Inactive Ingredients and Colors: The inactive ingredients in ADDERALL XR™ capsules include: gelatin capsules, hydroxypropyl methylcellulose, methacrylic acid copolymer, opadry beige, sugar spheres, talc, and triethyl citrate. Gelatin capsules contain edible inks, kosher gelatin, and titanium dioxide. The 5 mg, 10 mg, and 15 mg capsules also contain FD&C Blue #2. The 20 mg, 25 mg, and 30 mg capsules also contain red iron oxide and yellow iron oxide.

CLINICAL PHARMACOLOGY

Pharmacodynamics

Amphetamines are non-catecholamine sympathomimetic amines with CNS stimulant activity. The mode of therapeutic action in Attention Deficit Hyperactivity Disorder (ADHD) is not known. Amphetamines are thought to block the reuptake of norepinephrine and dopamine into the presynaptic neuron and increase the release of these monoamines into the extraneuronal space.

Pharmacokinetics

Pharmacokinetic studies of ADDERALL XR™ have been conducted in healthy adult and pediatric (6-12 yrs) subjects, and pediatric patients with ADHD. Both ADDERALL® (immediate-release) tablets and ADDERALL XR™ capsules contain d-amphetamine and l-amphetamine salts in the ratio of 3:1. Following administration of ADDERALL® (immediate-release), the peak plasma concentrations occurred in about 3 hours for both d-amphetamine and l-amphetamine.

The time to reach maximum plasma concentration (T_{max}) for ADDERALL XR™ is about 7 hours, which is about 4 hours longer compared to ADDERALL® (immediate-release). This is consistent with the extended-release nature of the product.

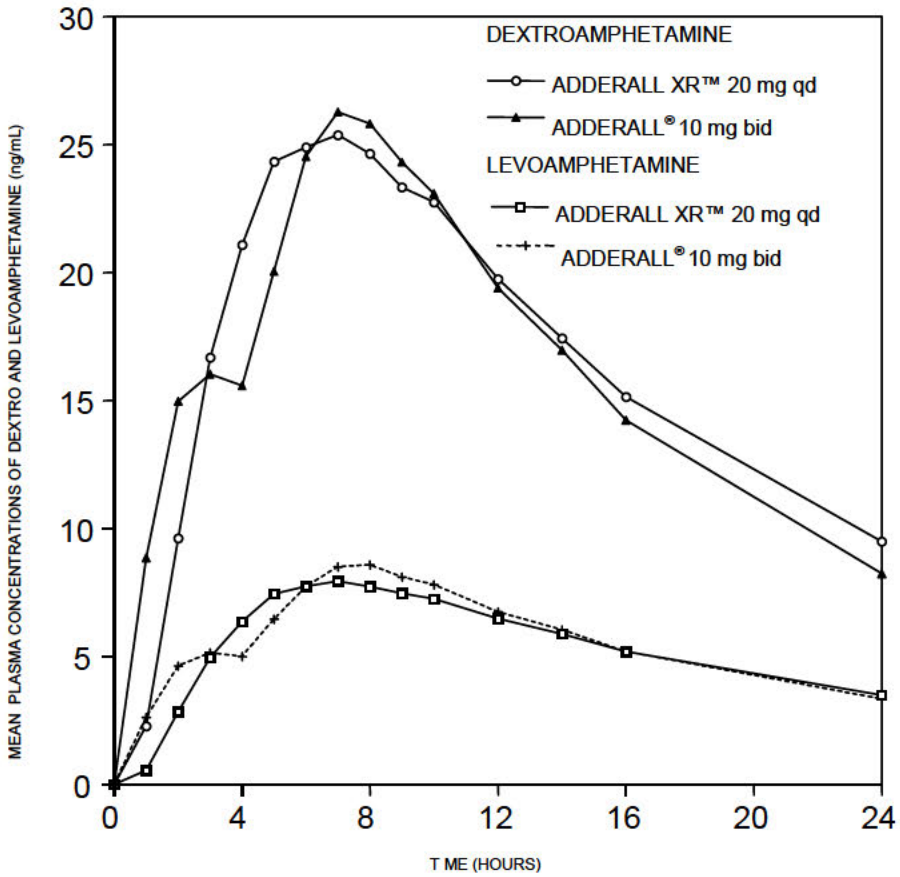


Figure 1 Mean d-amphetamine and l-amphetamine plasma concentrations following administration of ADDERALL XR™ 20 mg (8am) and ADDERALL® (immediate-release) 10 mg bid (8am and 12 noon) in the fed state.

A single dose of ADDERALL XR™ 20 mg capsules provided comparable plasma concentration profiles of both d-amphetamine and l-amphetamine to ADDERALL® (immediate-release) 10 mg bid administered 4 hours apart.

The mean elimination half-lives for d-amphetamine and l-amphetamine in adults are 10 hours and 13 hours, respectively. In children aged 6 to 12 years, the mean elimination half-life is 1 hour shorter for d-amphetamine (9 hours) and 2 hours shorter for l-amphetamine (11 hours). Children had higher systemic exposure to amphetamine (C_{max} and AUC) than adults for a given dose of ADDERALL XR®, which was attributed to the higher dose administered to children on a mg/kg body weight basis compared to adults. Upon dose normalization on a mg/kg basis, children showed 30% less systemic exposure compared to adults.

ADDERALL XR® demonstrates linear pharmacokinetics over the dose range of 20 to 60 mg in adults and 5 to 30 mg in children aged 6 to 12 years. There is no unexpected accumulation at steady state in children.

Food does not affect the extent of absorption of d-amphetamine and l-amphetamine, but prolongs T_{max} by 2.5 hours (from 5.2 hrs at fasted state to 7.7 hrs after a high-fat meal for d-amphetamine and 2.1 hours (from 5.6 hrs at fasted state to 7.7 hrs after a high fat meal) for l amphetamine after administration of Adderall XR 30-mg. Opening the capsule and sprinkling the contents on applesauce results in comparable absorption to the intact capsule taken in the fasted state. Equal doses of ADDERALL XR strengths are bioequivalent.

Special Populations

Pediatric Patients
Children eliminated amphetamine faster than adults. The elimination half-life ($t_{1/2}$) is approximately 1 hour shorter for d-amphetamine and 2 hours shorter for l-amphetamine in children than in adults. However, children had higher systemic exposure to amphetamine (C_{max} and AUC) than adults for a given dose of ADDERALL XR™, which was attributed to the higher dose administered to children on a mg/kg body weight basis compared to adults. Upon dose normalization on a mg/kg basis, children showed 30% less systemic exposure compared to adults.

Gender
Systemic exposure to amphetamine was 20-30% higher in women (N=20) than in men (N=20) due to the higher dose administered to women on a mg/kg body weight basis. When the exposure parameters (C_{max} and AUC) were normalized by dose (mg/kg), these differences diminished.

Race
Formal pharmacokinetic studies for race have not been conducted. However, amphetamine pharmacokinetics appeared to be comparable among Caucasians (N=33), Blacks (N=8) and Hispanics (N=10).

Clinical Trials
Children
A double-blind, randomized, placebo-controlled, parallel-group study was conducted in children aged 6-12 (N=584) who met DSM-IV criteria for ADHD (either the combined type or the hyperactive-impulsive type). Patients were randomized to fixed dose treatment groups receiving final doses of 10, 20, or 30 mg of ADDERALL XR™ or placebo once daily in the morning for three weeks. Significant improvements in patient behavior, based upon teacher ratings of attention and hyperactivity, were observed for all ADDERALL XR™ doses compared to patients who received placebo, for all three weeks, including the first week of treatment, when all ADDERALL XR™ subjects were receiving a dose of 10 mg/day. Patients who received ADDERALL XR™ showed behavioral improvements in both morning and afternoon assessments compared to patients on placebo.

In a classroom analogue study, patients (N=51) receiving fixed doses of 10 mg, 20 mg or 30 mg ADDERALL XR™ demonstrated statistically significant improvements in teacher-rated behavior and performance measures, compared to patients treated with placebo.

Adults
A double-blind, randomized, placebo-controlled, parallel-group study was conducted in adults (N=255) who met DSM-IV-TR criteria for ADHD. Patients were randomized to fixed dose treatment groups receiving final doses of 20, 40, or 60 mg of ADDERALL XR® or placebo once daily in the morning for four weeks. Significant improvements, measured with the Attention Deficit Hyperactivity Disorder-Rating Scale (ADHD-RS), an 18-item scale that measures the core symptoms of ADHD symptoms, were observed at endpoint for all ADDERALL XR® doses compared to patients who received placebo for all four weeks. There was not adequate evidence that doses greater than 20 mg/day conferred additional benefit.

INDICATIONS
ADDERALL XR™ is indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD).

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 and one controlled trial in adults who met DSM-IV criteria for ADHD (see CLINICAL PHARMACOLOGY), along with extrapolation from the known efficacy of ADDERALL®, the immediate-release formulation of this substance.

A diagnosis of Attention Deficit Hyperactivity Disorder (ADHD; DSM-IV) implies the presence of hyperactive-impulsive or inattentive symptoms that caused impairment and were present before age 7 years. The symptoms must cause clinically significant impairment, e.g., in social, academic, or occupational functioning, and be present in two 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 six 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. For the Hyperactive-Impulsive Type, at least six of the following symptoms must have persisted for at least 6 months: fidgeting/squirming; leaving seat; inappropriate running/climbing; difficulty with quiet activities; "on the go;" excessive talking; blurting answers; can't wait turn; intrusive. The Combined Type requires both inattentive and hyperactive-impulsive criteria to be met.

Special Diagnostic Considerations: Specific etiology of this syndrome is unknown, and there is no single diagnostic test. Adequate diagnosis requires the use not only of medical but 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 child and not solely on the presence of the required number of DSM-IV characteristics.

Need for Comprehensive Treatment Program: ADDERALL XR™ 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 children with this syndrome. Stimulants are not intended for use in the child who exhibits symptoms secondary to environmental factors and/or other primary psychiatric disorders, including psychosis. Appropriate educational placement is essential and psychosocial intervention is often helpful. When remedial measures alone are insufficient, the decision to prescribe stimulant medication will depend upon the physician's assessment of the chronicity and severity of the child's symptoms.

Long-Term Use: The effectiveness of ADDERALL XR™ for long-term use, i.e., for more than 3 weeks in children and 4-weeks in adults, has not been systematically evaluated in controlled trials. Therefore, the physician who elects to use ADDERALL XR™ for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient.

CONTRAINDICATIONS

Advanced arteriosclerosis, symptomatic cardiovascular disease, moderate to severe hypertension, hyperthyroidism, known hypersensitivity or idiosyncrasy to the sympathomimetic amines, glaucoma.

Agitated states.

Patients with a history of drug abuse.

During or within 14 days following the administration of monoamine oxidase inhibitors (hypertensive crises may result).

WARNINGS

Psychosis: Clinical experience suggests that, in psychotic patients, administration of amphetamine may exacerbate symptoms of behavior disturbance and thought disorder.

Long-Term Suppression of Growth: Data are inadequate to determine whether chronic use of stimulants in children, including amphetamine, may be causally associated with suppression of growth. Therefore, growth should be monitored during treatment, and patients who are not growing or gaining weight as expected should have their treatment interrupted.

Sudden Death and Pre-existing Structural Cardiac Abnormalities: Sudden death has been reported in association with amphetamine treatment at usual doses in children with structural cardiac abnormalities. Adderall XR generally should not be used in children or adults with structural cardiac abnormalities.

PRECAUTIONS

General: The least amount of amphetamine feasible should be prescribed or dispensed at one time in order to

minimize the possibility of overdosage.

Hypertension: Caution is to be exercised in prescribing amphetamines for patients with even mild hypertension (see CONTRAINDICATIONS). Blood pressure and pulse should be monitored at appropriate intervals in patients taking ADDERALL XR™, especially patients with hypertension.

Tics: Amphetamines have been reported to exacerbate motor and phonic tics and Tourette's syndrome. Therefore, clinical evaluation for tics and Tourette's syndrome in children and their families should precede use of stimulant medications.

Information for Patients: Amphetamines may impair the ability of the patient to engage in potentially hazardous activities such as operating machinery or vehicles; the patient should therefore be cautioned accordingly.

Drug Interactions: *Acidifying agents* -Gastrointestinal acidifying agents (guanethidine, reserpine, glutamic acid HCI, ascorbic acid, etc.) lower absorption of amphetamines.
Urinary acidifying agents -These agents (ammonium chloride, sodium acid phosphate, etc.) increase the concentration of the ionized species of the amphetamine molecule, thereby increasing urinary excretion. Both groups of agents lower blood levels and efficacy of amphetamines.
Adrenergic blockers -Adrenergic blockers are inhibited by amphetamines.
Alkalinizing agents -Gastrointestinal alkalinizing agents (sodium bicarbonate, etc.) increase absorption of amphetamines. Co-administration of ADDERALL XR™ and gastrointestinal alkalinizing agents, such as antacids, should be avoided. Urinary alkalinizing agents (acetazolamide, some thiazides) increase the concentration of the non-ionized species of the amphetamine molecule, thereby decreasing urinary excretion. Both groups of agents increase blood levels and therefore potentiate the actions of amphetamines.
Antidepressants, tricyclic -Amphetamines may enhance the activity of tricyclic antidepressants or sympathomimetic agents; d-amphetamine with desipramine or protriptyline and possibly other tricyclics cause striking and sustained increases in the concentration of d-amphetamine in the brain;
cardiovascular effects can be potentiated.
MAO inhibitors -MAOI antidepressants, as well as a metabolite of furazolidone, slow amphetamine metabolism. This slowing potentiates amphetamines, increasing their effect on the release of norepinephrine and other monoamines from adrenergic nerve endings; this can cause headaches and other signs of hypertensive crisis. A variety of toxic neurological effects and malignant hyperpyrexia can occur, sometimes with fatal results.
Antihistamines -Amphetamines may counteract the sedative effect of antihistamines.
Antihypertensives -Amphetamines may antagonize the hypotensive effects of antihypertensives.
Chlorpromazine -Chlorpromazine blocks dopamine and norepinephrine receptors, thus inhibiting the central stimulant effects of amphetamines, and can be used to treat amphetamine poisoning.
Ethosuximide -Amphetamines may delay intestinal absorption of ethosuximide.
Haloperidol -Haloperidol blocks dopamine receptors, thus inhibiting the central stimulant effects of amphetamines.
Lithium carbonate -The anorectic and stimulatory effects of amphetamines may be inhibited by lithium carbonate.
Meperidine -Amphetamines potentiate the analgesic effect of meperidine.
Methenamine therapy -Urinary excretion of amphetamines is increased, and efficacy is reduced, by acidifying agents used in methenamine therapy.
Norepinephrine -Amphetamines enhance the adrenergic effect of norepinephrine.
Phenobarbital -Amphetamines may delay intestinal absorption of phenobarbital; co-administration of phenobarbital may produce a synergistic anticonvulsant action.
Phenytoin -Amphetamines may delay intestinal absorption of phenytoin; co-administration of phenytoin may produce a synergistic anticonvulsant action.
Propoxyphene -In cases of propoxyphene overdosage, amphetamine CNS stimulation is potentiated and fatal convulsions can occur.
Veratrum alkaloids -Amphetamines inhibit the hypotensive effect of veratrum alkaloids.

Drug/Laboratory Test Interactions: Amphetamines can cause a significant elevation in plasma corticosteroid levels. This increase is greatest in the evening. Amphetamines may interfere with urinary steroid determinations.

Carcinogenesis/Mutagenesis and Impairment of Fertility: No evidence of carcinogenicity was found in studies in which d,l-amphetamine (enantiomer ratio of 1:1) was administered to mice and rats in the diet for 2 years at doses of up to 30 mg/kg/day in male mice, 19 mg/kg/day in female mice, and 5 mg/kg/day in male and female rats. These doses are approximately 2.4, 1.5, and 0.8 times, respectively, the maximum recommended human dose of 30 mg/day [child] on a mg/m ^{2} body surface area basis.

Amphetamine, in the enantiomer ratio present in ADDERALL® (immediate-release)(d- to l- ratio of 3:1), was not clastogenic in the mouse bone marrow micronucleus test *in vivo* and was negative when tested in the E. coli component of the Ames test *in vitro*. d,l-Amphetamine (1:1 enantiomer ratio) has been reported to produce a positive response in the mouse bone marrow micronucleus test, an equivocal response in the Ames test, and negative responses in the *in vitro* sister chromatid exchange and chromosomal aberration assays.
Amphetamine, in the enantiomer ratio present in ADDERALL® (immediate-release)(d- to l- ratio of 3:1), did not adversely affect fertility or early embryonic development in the rat at doses of up to 20 mg/kg/day (approximately 5 times the maximum recommended human dose of 30 mg/day on a mg/m^2 body surface area basis).

Pregnancy: Pregnancy Category C. Amphetamine, in the enantiomer ratio present in ADDERALL® (d- to l- ratio of 3:1), had no apparent effects on embryofetal morphological development or survival when orally administered to pregnant rats and rabbits throughout the period of organogenesis at doses of up to 6 and 16 mg/kg/day, respectively. These doses are approximately 1.5 and 8 times, respectively, the maximum recommended human dose of 30 mg/day [child] on a mg/m^2 body surface area basis. Fetal malformations and death have been reported in mice following parenteral administration of d-amphetamine doses of 50 mg/kg/day (approximately 6 times that of a human dose of 30 mg/day [child] on a mg/m^2 basis) or greater to pregnant animals. Administration of these doses was also associated with severe maternal toxicity.

A number of studies in rodents indicate that prenatal or early postnatal exposure to amphetamine (d- or d,l-), at doses similar to those used clinically, can result in long-term neurochemical and behavioral alterations. Reported behavioral effects include learning and memory deficits, altered locomotor activity, and changes in sexual function.

There are no adequate and well-controlled studies in pregnant women. There has been one report of severe congenital bony deformity, tracheo-esophageal fistula, and anal atresia (vater association) in a baby born to a woman who took dextroamphetamine sulfate with lovastatin during the first trimester of pregnancy. Amphetamines should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects: Infants born to mothers dependent on amphetamines have an increased risk of premature delivery and low birth weight. Also, these infants may experience symptoms of withdrawal as demonstrated by dysphoria, including agitation, and significant lassitude.

Usage in Nursing Mothers: Amphetamines are excreted in human milk. Mothers taking amphetamines should be advised to refrain from nursing.

Pediatric Use: ADDERALL XR™ is indicated for use in children 6 years of age and older.

Use in Children Under Six Years of Age: Effects of ADDERALL XR™ in 3-5 year olds have not been studied. Long-term effects of amphetamines in children have not been well established. Amphetamines are not recommended for use in children under 3 years of age.

Geriatric Use: ADDERALL XR™ has not been studied in the geriatric population.

ADVERSE EVENTS

The premarketing development program for ADDERALL XR™ included exposures in a total of 965 participants in clinical trials (635 pediatric patients, 248 adult patients and 82 healthy adult subjects). Of these, 635 patients (ages 6 to 12) were evaluated in two controlled clinical studies, and one open-label clinical study, and two single-dose clinical pharmacology studies (N= 40). Safety data on all patients are included in the discussion that follows. Adverse reactions were assessed by collecting adverse events, results of physical examinations, vital signs, weights, laboratory analyses, and ECGs.

Adverse events during exposure were obtained primarily by general inquiry and recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of events into a smaller number of standardized event categories. In the tables and listings that follow, COSTART terminology has been used to classify reported adverse events.

The stated frequencies of adverse events represent the proportion of individuals who experienced, at least once, a treatment-emergent adverse event of the type listed.

Adverse events associated with discontinuation of treatment: In two placebo-controlled studies of up to 5 weeks duration among children with ADHD, 2.4% (10/425) of ADDERALL XR™ treated patients discontinued due to adverse events (including 3 patients with loss of appetite, one of whom also reported insomnia) compared to 2.7% (7/259) receiving placebo. The most frequent adverse events associated with discontinuation of ADDERALL XR™ in controlled and uncontrolled, multiple-dose clinical trials of pediatric patients (N=595) are presented below. Over half of these patients were exposed to ADDERALL XR™ for 12 months or more.

Adverse event	% of pediatric patients discontinuing (n=595)
Anorexia (loss of appetite)	2.9
Insomnia	1.5
Weight loss	1.2
Emotional lability	1.0
Depression	0.7

In one placebo-controlled 4-week study among adults with ADHD, patients who discontinued treatment due to adverse events among ADDERALL XR®-treated patients (N=191) were 3.1% (n=6) for nervousness including anxiety and irritability, 2.6% (n=5) for insomnia, 1% (n=2) each for headache, palpitation, and somnolence; and, 0.5% (n=1) each for ALT increase, agitation, chest pain, cocaine craving, elevated blood pressure, and weight loss.

Adverse events occurring in a controlled trial: Adverse events reported in a 3-week clinical trial of pediatric patients and a 4-week clinical trial in adults treated with ADDERALL XR™ or placebo are presented in the tables below.

The prescriber should be aware that these figures cannot be used to predict the incidence of adverse events in the course of usual medical practice where patient characteristics and other factors differ from those which prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and non-drug factors to the adverse event incidence rate in the population studied.

Table 1 Adverse Events Reported by More Than 1% of Pediatric Patients Receiving ADDERALL XR™ with Higher Incidence Than on Placebo in a 584 Patient Clinical Study

Body System	Preferred Term	SLI 381 (n=374)	Placebo (n=210)
General	Abdominal Pain (stomachache)	14%	10%
	Accidental Injury	3%	2%
	Asthenia (fatigue)	2%	0%
	Fever	5%	2%
	Infection	4%	2%
	Viral Infection	2%	0%
Digestive System	Loss of Appetite	22%	2%
	Diarrhea	2%	1%
	Dyspepsia	2%	1%
	Nausea	5%	3%
	Vomiting	7%	4%
Nervous System	Dizziness	2%	0%
	Emotional Lability	9%	2%
	Insomnia	17%	2%
	Nervousness	6%	2%
Metabolic/Nutritional	Weight Loss	4%	0%

Table 2 Adverse Events Reported by 5% or More of Adults Receiving ADDERALL XR® with Higher Incidence Than on Placebo in a 255 Patient Clinical Forced Weekly-Dose Titration Study*

Body System	Preferred Term	ADDERALL XR® (n=191)	Placebo (n=64)
General	Asthenia	6%	5%
	Headache	26%	13%
Digestive System	Loss of Appetite	33%	3%
	Diarrhea	6%	0%
	Dry Mouth	35%	5%
	Nausea	8%	3%
Nervous System	Agitation	8%	5%
	Anxiety	8%	5%
	Dizziness	7%	0%
	Insomnia	27%	13%
Cardiovascular System	Tachycardia	6%	3%
Metabolic/Nutritional	Weight Loss	11%	0%
Urogenital System	Urinary Tract Infection	5%	0%

Note: The following events did not meet the criterion for inclusion in Table 2 but were reported by 2% to 4% of adult patients receiving ADDERALL XR® with a higher incidence than patients receiving placebo in this study: infection, photosensitivity reaction, constipation, tooth disorder, emotional lability, libido decreased, somnolence, speech disorder, palpitation, twitching, dyspnea, sweating, dysmenorrhea, and impotence.

*included doses up to 60 mg.

The following adverse reactions have been associated with amphetamine use:

Cardiovascular: Palpitations, tachycardia, elevation of blood pressure, sudden death, myocardial infarction. There have been isolated reports of cardiomyopathy associated with chronic amphetamine use.

Central Nervous System: Psychotic episodes at recommended doses, overstimulation, restlessness, dizziness, insomnia, euphoria, dyskinesia, dysphoria, depression, tremor, headache, exacerbation of motor and phonic tics and Tourette's syndrome, seizures, stroke.

Gastrointestinal: Dryness of the mouth, unpleasant taste, diarrhea, constipation, other gastrointestinal disturbances. Anorexia and weight loss may occur as undesirable effects.

Allergic: Urticaria.

Endocrine: Impotence, changes in libido.

DRUG ABUSE AND DEPENDENCE

ADDERALL XR™ is a Schedule II controlled substance.

Amphetamines have been extensively abused. Tolerance, extreme psychological dependence, and severe social disability have occurred. There are reports of patients who have increased the dosage to many times that recommended. Abrupt cessation following prolonged high dosage administration results in extreme fatigue and mental depression; changes are also noted on the sleep EEG. Manifestations of chronic intoxication with amphetamines may include severe dermatoses, marked insomnia, irritability, hyperactivity, and personality changes. The most severe manifestation of chronic intoxication is psychosis, often clinically indistinguishable from schizophrenia.

OVERDOSAGE

Individual patient response to amphetamines varies widely. Toxic symptoms may occur idiosyncratically at low doses.

Symptoms: Manifestations of acute overdosage with amphetamines include restlessness, tremor, hyperreflexia, rapid respiration, confusion, assaultiveness, hallucinations, panic states,
hyperpyrexia and rhabdomyolysis. Fatigue and depression usually follow the central nervous system stimulation. Cardiovascular effects include arrhythmias, hypertension or hypotension and circulatory collapse. Gastrointestinal symptoms include nausea, vomiting, diarrhea, and abdominal cramps. Fatal poisoning is usually preceded by convulsions and coma.

Treatment: Consult with a Certified Poison Control Center for up to date guidance and advice. Management of acute amphetamine intoxication is largely symptomatic and includes gastric lavage, administration of activated charcoal, administration of a cathartic and sedation. Experience with hemodialysis or peritoneal dialysis is inadequate to permit recommendation in this regard. Acidification of the urine increases amphetamine excretion, but is believed to increase risk of acute renal failure if myoglobinuria is present. If acute severe hypertension complicates amphetamine overdosage, administration of intravenous phentolamine has been suggested. However, a gradual drop in blood pressure will usually result when sufficient sedation has been achieved. Chlorpromazine antagonizes the central stimulant effects of amphetamines and can be used to treat amphetamine intoxication.

The prolonged release of mixed amphetamine salts from ADDERALL XR™ should be considered when treating patients with overdose.

DOSAGE AND ADMINISTRATION

Dosage should be individualized according to the therapeutic needs and response of the patient.
ADDERALL XR® should be administered at the lowest effective dosage.

Children

In children with ADHD who are 6 years of age and older and are either starting treatment for the first time or switching from another medication, start with 10 mg once daily in the morning; daily dosage may be adjusted in increments of 5 mg or 10 mg at weekly intervals. When in the judgement of the clinician a lower initial dose is appropriate, patients may begin treatment with 5 mg once daily in the morning. The maximum recommended dose for children is 30 mg/day; doses greater than 30 mg/day of ADDERALL XR™ have not been studied in children. Amphetamines are not recommended for children under 3 years of age. ADDERALL XR™ has not been studied in children under 6 years of age.

Adults

In adults with ADHD who are either starting treatment for the first time or switching from another medication, the recommended dose is 20 mg/day.

Patients Currently Using ADDERALL®- Based on bioequivalence data, patients taking divided doses of immediate-release ADDERALL®, for example twice a day, may be switched to ADDERALL XR™ at the same

total daily dose taken once daily. Titrate at weekly intervals to appropriate efficacy and tolerability as indicated.

ADDERALL XR™ capsules may be taken whole, or the capsule may be opened and the entire contents sprinkled on applesauce. If the patient is using the sprinkle administration method, the sprinkled applesauce should be consumed immediately; it should not be stored. Patients should take the applesauce with sprinkled beads in its entirety without chewing. The dose of a single capsule should not be divided. The contents of the entire capsule should be taken, and patients should not take anything less than one capsule per day.

ADDERALL XR may be taken with or without food.

ADDERALL XR™ should be given upon awakening. Afternoon doses should be avoided because of the potential for insomnia.

Where possible, drug administration should be interrupted occasionally to determine if there is a recurrence of behavioral symptoms sufficient to require continued therapy**.**

HOW SUPPLIED:
ADDERALL XR® 5 mg Capsules: Clear/blue (imprinted ADDERALL XR 5 mg), bottles of 100, NDC 54092-381-01
ADDERALL XR® 10 mg Capsules: Blue/blue (imprinted ADDERALL XR 10 mg), bottles of 100, NDC 54092-383-01
ADDERALL XR® 15 mg Capsules: Blue/white (imprinted ADDERALL XR 15 mg), bottles of 100, NDC 54092-385-01
ADDERALL XR® 20 mg Capsules: Orange/orange (imprinted ADDERALL XR 20 mg), bottles of 100, NDC 54092-387-01
ADDERALL XR® 25 mg Capsules: Orange/white (imprinted ADDERALL XR 25 mg), bottles of 100, NDC 54092-389-01
ADDERALL XR® 30 mg Capsules: Natural/orange (imprinted ADDERALL XR 30 mg), bottles of 100, NDC 54092-391-01

Dispense in a tight, light-resistant container as defined in the USP.
Store at 25º C (77º F). Excursions permitted to 15-30º C (59-86º F) [see USP Controlled Room Temperature]

ANIMAL TOXICOLOGY
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.

Manufactured by Catalytica Pharmaceuticals Inc., Greenville, North Carolina 27835. Distributed and marketed by Shire US Inc., Florence, KY 41042

For more information call 1-800-536-7878 or visit www.adderallxr.com

ADDERALL® is registered in the US Patent and Trademark Office

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

021303Orig1s005

SUMMARY REVIEW

MEMORANDUM

DATE: August 8, 2004

FROM: Director
Division of Neuropharmacological Drug Products/HFD-120

TO: File, NDA 21-303/S-005 (b) (4)

SUBJEC: Action memo for NDA 21-303/S-005 (b) (4) for the use of Adderall XR in Attention Deficit Hyperactivity Disorder (ADHD) in Adults

NDA 21-303/S-005, for the use of Adderall XR in Attention Deficit Hyperactivity Disorder (ADHD) in Adults, was submitted by Shire Pharmaceutical Development, Inc., on 12/18/02. This application contained the results of a single study in which patients were randomized to fixed doses of 20 mg, 40 mg, and 60 mg, or placebo. (b) (4) The division issued an Approvable letter on 10/17/03, in which we informed the sponsor that we had concluded that the study did not provide evidence that doses greater than 20 mg conferred any additional benefit, and that the recommended dose would be 20 mg. (b) (4), (b) (4) In addition, we asked the sponsor to address several safety issues, including dose response for vital signs, EKG findings, clarification of the number of patients exposed at given doses, and an analysis of post-marketing reports of MIs, CVAs, sudden deaths, seizures, non-fatal arrhythmias, cardiomyopathy, and ischemic organ damage. Further, we expressed concerns that adverse events in general were not reported adequately. Finally, we had some additional clinical pharmacology questions.

The sponsor responded in a submission dated 2/13/04. The response included the requested analyses and, in addition, the sponsor provided a re-analysis of the clinical tria (b) (4). The re-submission has been reviewed by Dr. Teresa Podruchny, medical officer (review dated 8/3/04), Dr. Tristan Massie, statistician (review dated 7/16/04), Dr. Lisa Jones, safety team medical officer, Dr. Kofi Kumi, Office of Clinical Pharmacology and Biopharmaceutics (review dated 6/21/04), and Dr. Paul Andreason, psychiatric drugs team leader (memo dated 8/3/04). The review team recommends that the application be approved, pending agreement with the sponsor on labeling (although Dr. Kumi finds one of the sponsor's responses unacceptable, this issue is moot; see below).

No identified safety signal would preclude approval. Dr. Podruchny has reviewed the sponsor's analyses of the NDA data, and Dr. Jones has reviewed the post-marketing reports. None of the latter establish that amphetamines increase the

rate of serious cardiovascular adverse events above those seen in the background population, although there was a suggestion that the use of stimulants in patients with underlying structural cardiac abnormalities is particularly dangerous (six of twelve sudden pediatric deaths occurred in patients with underlying cardiac abnormalities or a family history of arrhythmias).

In addition, Dr. Podruchny found no important dose related vital sign or EKG abnormalities, and, concluded that, in general, the sponsor did, in fact, adequately record and report adverse events.

(b) (4)

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In particular, they performed analyses in which patients were assigned the dose that they ultimately achieved, rather than the dose to which they were randomized. As Dr. Massie points out, this approach is flawed for at least two reasons.

First, this results in an analysis of non-randomized groups. Second, patients in all dose groups continue to improve throughout the entire 4 weeks of the study. By including patients in the dose group defined by the dose they actually received (instead of the group to which they were randomized), patients now assigned to the lower dose groups will have been in the study shorter durations than those who achieved the higher dose(s). This will bias the results in favor of the higher doses, because those patients will have been in the study longer (and we know that longer duration in the study, by itself, is associated with improvement).

The sponsor also presented these analyses for patients in the group defined by a baseline score on the ADHD-RS (primary outcome) of at least 32 (the median score). (b) (4) We have no evidence that this analysis was pre-specified (it was not submitted to the protocol), although the sponsor asserts (in several telephone conversations) that they did "prospectively" identify this analysis, prior to breaking the blind, but knowing the median baseline score. In any event, as Dr. Massie notes, this analysis also confounds dose and time in study. Further, as Dr. Massie describes, he performed a linear trend analysis of this subgroup, counting patients in the dose group to which they had been randomized; although he determined a p-value of 0.06, he also determined a p-value of 0.07 in the negative direction for those with a baseline score of less than 32.

The sponsor also submitted additional analyses (examining incremental changes from the preceding week, proportions of patients much improved or very much improved on the CGI-I) that included patients in their actual achieved-dose

group, as in the previous analyses. As in the previous analyses, these analyses were post hoc, and, importantly, also confounded time-in-study and dose.

For these reasons, I have concluded that the application should be approved, with labeling that states that doses greater than 20 mg/day (in adults) confer no additional benefit, and that 20 mg/day is the recommended dose. (b) (4) herefore, I will issue the attached Approval letter, with appended labeling (the language of which has been agreed to by the sponsor_.

Russell Katz, M.D.

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

/s/

Russell Katz
8/11/04 10:55:03 AM
MEDICAL OFFICER

,MEMORANDUM

DATE: October 17, 2003

FROM: Director
Division of Neuropharmacological Drug Products/HFD-120

TO: File, NDA 21-303/S-005 & (b) (4)

SUBJECT: Action Memo for NDA 21-303/S-005 and (b) (4), for the use of Adderall XR in the treatment of adults with Attention Deficit Hyperactivity Disorder (ADHD)

NDA 21-303/S-005 and (b) (4), for the use of Adderall XR (a once daily extended release formulation of Adderall, a combination of mixed salts of amphetamine) in the treatment of adults with Attention Deficit Hyperactivity Disorder (ADHD), was submitted by Shire Pharmaceuticals Development Inc., on 12/18/02. Adderall XR is currently approved for the treatment of ADHD in pediatric and adolescent patients. The initial application proposed a 20 mg and (b) (4)

The 12/18/02 submission contained the results of a single randomized controlled trial in adults with ADHD (Study 303) and an open label safety extension study (Study 304). In addition, it contained data from several single and multiple dose pharmacokinetic (PK) studies, (b) (4) (b) (4) The application has been reviewed by Dr. Glenn Mannheim, medical officer (review dated 10/9/03), Dr. Tristan Massie, statistician (review dated 7/22/03), Dr. Kofi Kumi, Office of Clinical Pharmacology and Biopharmaceutics (review dated 8/4/03), Dr. Chhagan Tele, chemist (review dated 8/15/03), Dr. Kate Gelperin, Office of Drug Safety (review dated 9/23/03), Dr. Ni Khin, Division of Scientific Investigations (review dated 7/29/03), and Dr. Paul Andreason, Psychiatric Drugs Team Leader (memo dated 10/9/03). The clinical team recommends that the application be considered Approvable.

I will briefly describe the relevant data and offer the rationale for the Division's decision.

Efficacy

Study 303

This was a randomized multi-center trial in which adults with ADHD were randomized to treatment with placebo, Adderall XR 20 mg QD, 40 mg QD, or 60 mg QD. The treatment period was 1-6 weeks; all patients were started at 20 mg

QD, and patients randomized to higher doses achieved those doses with a 10 mg QD increment/week, so that patients randomized to 60 mg QD received that dose for 4 weeks. The primary outcome measure was change from baseline in the ADHD-RD, an 18 item scale consisting of items relating to hyperactivity/impulsivity and inattention. The scale has primarily been used in studies of pediatric patients, and has a few items that seem to be more specifically geared to school behavior; most items, however, are clearly applicable to adults, although the scale has not been validated in adults. Each item is scored from 0 (normal) to 3 (severe symptoms). The assessment was made weekly, as were several other secondary outcome assessments.

The following chart displays the results of the analysis of the primary outcome for the intent to treat population using the last observation carried forward (LOCF).

Dose	Change from Baseline (LS Mean, Pbo adjusted)	P-value
20 mg QD (N=64)	-6.6	0.001
40 mg QD (N=64)	-7.2	<0.001
60 mg QD (N=60)	-7.8	<0.001

While there is an apparent numerical increase in treatment effect with dose, as Dr. Massie points out (page 16 of his review), these differences are small compared to the variability of the data. For example, he notes that the 95% confidence intervals surrounding each of the estimates of the treatment effect contain all three LS Means. Further, he performed additional modeling that further confirmed that there was no dose response trend.

Safety

Drs. Mannheim and Andreason have described the relevant safety data in considerable detail. The sponsor has submitted safety data on a total of 280 patients at any dose. As Dr. Mannheim describes, at a meeting with the sponsor prior to submission of the NDA, we expected that they would submit data in about 200 patients treated for at least 6 months at therapeutic doses. It is unfortunately impossible to determine how many patients were treated for at least 6 months at any dose, but it appears that only 19 patients have been treated for this duration at the highest dose shown to be effective, 60 mg QD.

There were no deaths in the development program, and there were a total of six (6) serious adverse events in Studies 303 and 304. A total of 12% of drug treated patients and 1.6% of placebo patients discontinued treatment in Study 303 due to adverse events; 17% of patients discontinued treatment in Study 304.

About 85% of drug treated and 56% of placebo-treated patients reported an adverse event in Study 303. In general, the adverse events seen in this database were those expected with stimulants (anorexia, insomnia, nervousness, weight loss, etc). There was also a fairly high incidence of dry mouth and headache. There was little evidence of a dose response for most ADRs.

Following is a display of mean changes from baseline in vital signs, followed by the results of an outlier analysis:

	Drug	Placebo
Change in Systolic BP (mm Hg)	1.9	-1.9
Change in Diastolic BP (mm Hg)	2.5	2.1
Change in Pulse (bpm)	5.2	1.9
Change in Weight (lbs)	-4.5	0.2
Systolic HTN (> 160 mm Hg)	2%	0
Diastolic HTN (>90 mm Hg)	22%	20%
Tachycardia (>100 bpm)	15%	8.3%

The sponsor has also presented mean changes in blood pressure by dose, with the greatest change from baseline occurring in the 40 mg/day group:

Dose	Mean Change in SBP (mm Hg)	Mean Change in DBP (mm Hg)
Pbo	None	None
20 mg	0.96	None
40 mg	5.9	2.3
60 mg	2.2	1.8

These changes represent the maximum mean changes seen in any week (readings were taken weekly).

Dr. Mannheim also notes changes in mood, as judged by changes on the HAM-A and HAM-D. These changes are extremely small (although they reach statistical significance; see Dr. Andreason's memo, page 6).

Of particular concern to Dr. Mannheim is the occurrence of a number of serious adverse events (seizure, stroke, myocardial infarction, arrythmias, sudden death, and other events) that have occurred in relatively young patients (including pediatric patients) in the post-marketing setting (see, for example, the table on page 5 of Dr. Andreason's memo). Some of these events appear to have occurred in patients with no other known risk factors, and the events in general are those that could be the result of hemodynamic effects known to be

associated with stimulants (although these events, obtained in a search of the AERS database, were not necessarily seen with Adderall; the search was done to identify events seen in association with any amphetamine product).

The ODS review by Dr. Gelperin also concludes that these events can be plausibly related to treatment with Adderall, and recommends that additional evaluation of this issue, including consideration of a randomized controlled trial, should be pursued.

COMMENTS

The sponsor has submitted the results of a single controlled trial in adults with ADHD that demonstrates the effectiveness of 20, 40, and 60 mg QD. Dr. Mannheim notes that the primary outcome measure, the ADHD-RS, has not been shown to be valid in adults with ADHD, and this is technically true, but I agree with Dr. Andreason that the scale has face validity, there is no other better validated scale in adults, and the results of this trial demonstrate it to be sensitive to drug effect. For these reasons, I believe that the study demonstrates that Adderall XR is effective in the treatment of adult ADHD.

Dr. Mannheim has, based on his review of individual patient records, suggested that there are questions about the validity of the diagnosis of ADHD in some patients. For example, some subjects appeared to have been diagnosed with ADHD on the day of entry into the study (by definition, the symptoms of these patients must have begun prior to the age of 7 years, although the diagnosis need not have been made any minimum time prior to the study). I have discussed this point with the review team. I am convinced that, in general, the diagnoses were made adequately.

It is important to address the question of dose response in this study.

As noted above, there is an apparent dose response in the primary outcome measure. However, as Dr. Massie notes, this probably does not represent a true linear dose trend, for the reasons given above. Analyses done on the primary outcome measure excluding items 1, 3, 4, and 9 (the items deemed to be more relevant for the pediatric population) yielded no important dose response (see Dr. Mannheim's review, Table 13, page 163).

There was a dose-related numerical trend in the percentage of patients gauged to have improved, as assessed by the CGI, one of a list of secondary outcomes (23%, 30%, and 32% more improved patients compared to placebo for the 20, 40, and 60 mg/day groups, respectively). I have been unable to find, in any of the reviews, analyses of the other secondary measures.

Given these data, and our analyses, it is difficult to discern an important dose related increase in benefit. This becomes an important question in light of the potential for treatment with Adderall XR to cause serious adverse events.

Dr. Mannheim is very concerned about this potential. While I agree that the data (in particular the post-marketing data) raise the question about this potential, and these events are biologically plausible, given the pharmacology of the drug, I do not believe that we can yet come to any definitive conclusion about whether treatment with Adderall XR is associated with the serious outcomes reported to AERS. While it is of note that there seems to be no clear dose relatedness of adverse events in Study 303, it is also of note that analyses of critical cardiovascular data (blood pressure, pulse, QTc intervals, etc.) are not presented by dose. The sponsor should be required to do so, and, further, should be required to perform comprehensive and detailed analyses of the post-marketing data (including calculations of reporting rates and background rates of specific events of concern in a relevant population), in an attempt to answer the question of whether or not Adderall XR causes the serious events reported.

In regard to this latter point, Dr. Gelperin suggests that a controlled trial should be considered to address this question, and Drs. Mannheim and Andreason also suggest that this option should at least be considered.

This issue was discussed in a meeting on 10/10/03 with myself, Dr. Andreason, Dr. Mannheim, Dr. Tom Laughren (Psychiatric Drugs Team Leader), and Dr. Judy Racoosin (Safety Team Leader). We agreed, at least at this time, that such a study could not be reasonably performed, both because the duration and size of such a study would make it impractical, and it is not clear how it could be adequately controlled. In addition, both Drs. Mannheim and Andreason suggest that the issue of the long-term safety of this treatment in adults might be discussed at a public advisory committee meeting. I believe that this option, while perhaps ultimately reasonable, would not be useful until considerably more data and analyses are submitted by the sponsor.

It is also important to note that the sponsor appears to have submitted a paucity of long-term safety data, considerably less than we had been led to believe they would submit. In particular, it appears that only 19 patients have received 60 mg/day for at least 6 months (this appears to be true for the dose of 40 mg/day as well). The sponsor will have to submit more long-term data before this application may be approved.

In addition, Dr. Mannheim notes numerous discrepancies between the ADRs he found described in patient records and those actually reported in summary tables and/or narratives. This is particularly worrisome, and the sponsor must re-examine its database in order to assure us that they have accurately reported all adverse events.

Dr. Mannheim has made numerous recommendations related to further data he believes is needed and other actions (for example, the addition of a Boxed Warning to labeling at this time describing the occurrence of the serious ADRs noted above) that he concludes should be taken prior to approval.

I do not believe that most of these recommendations need be made at this time. In particular, I do not believe it would be prudent to include a Boxed Warning describing the events discussed above until (and unless) we have more information about the relationship between treatment with Adderall XR and these events. I do believe, however, that a number of Dr. Mannheim's requests for additional information should be transmitted to the sponsor (see the attached action letter for the specific requests).

There is a final issue that needs to be discussed.

(b) (4)

I agree with the review team that S-005 can be considered approvable at this time, but I also agree that considerable additional work needs to be performed before the application can be approved.

(b) (4)

Russell Katz, M.D.

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/s/

Russell Katz
10/17/03 11:48:00 AM
MEDICAL OFFICER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

021303Orig1s005

MEDICAL REVIEW(S)

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: August 3, 2004

FROM: Paul J. Andreason, M.D.
Team Leader, Psychiatric Drug Products
Division of Neuropharmacological Drug Products
HFD-120

SUBJECT: Recommendation for Approval Action for Adderall XR 20-mg in the Treatment of Adult ADHD

TO: File, NDA 21-303 S-005 (b) (4)
[Note: This memo should be filed with the February 13, 2004 Response to Approvable letter for this supplement.]

1.0 Background

NDA 21-303 Supplement 005 submitted on December 18, 2002 provided data to support a claim for Adderall XR in the treatment of Attention Deficit Hyperactive Disorder (ADHD) in the adult population (b) (4) . The Division of Neuropharmacological Drug Products (DNDP) issued an Approvable Action letter for Supplement 005 on October 17, 2003 to which Shire submitted a complete response on February 13, 2004. This memo reviews Shire's responses to the DNDP action letter of October 17, 2003. The Clinical and Safety review Teams met on September 2, 2004 to review and agree upon the attached clinical sections of draft labeling.

2.0 Chemistry

(b) (4)

3.0 Pharmacology/ Toxicology

Adderall XR is already a marketed product and is approved in the pediatric population. There were no pharmacology/ toxicology issues in the response submission.

4.0 Biopharmaceutics

The Office of Clinical Pharmacology and Biopharmaceutics (OCPB) review addressed Shire's responses to the clinical pharmacology questions in the October 17, 2003 action letter and provided draft labeling recommendations that were incorporated into the attached draft labeling. OCPB felt that the sponsor had adequately addressed their concerns except for OCPB question #2. OCPB requests

that Shire submit the control files and data files they used and that OCPB would also use to determine [redacted] (b) (4)

The reader will note that I removed the OCPB caveat from draft labeling that stated that [redacted] (b) (4)

5.0 Clinical

The primary clinical review of Shire's response was performed by Teresa Podruchny, MD. The review of Shire's epidemiological data and the consultative response from the Office of Drug Safety (ODS) was Lisa Jones, MD of the DNDP Safety Team. The primary statistical review was performed by Tristan Massie, PhD. ODS reviewed adverse event reports and provided an analysis of death and serious adverse cardiovascular events that were reported in patients in association with treatment with stimulants.

The following paragraphs summarize the responses to DNDP questions by number, Shire's responses, and the FDA reviewer conclusions and recommendations based on these responses:

Clinical Question #1-*Our review of Study 303 suggests that efficacy does not increase with doses greater than 20 mg/day. ...*

The Division stated that there did not seem to be evidence of increasing efficacy with increasing doses above 20-mg/day. DNDP asked that the sponsor provide further analysis that might suggest that doses above 20-mg added clinically significant benefit to treatment. The sponsor provided both an observed case (OC) analysis and an analysis of patients' actual dose versus clinical response to support the assertion that increasing doses provided clinical benefit above that which was seen at the 20-mg dose.

Neither Drs. Massie nor Podruchny felt that there was sufficient evidence to approve doses of greater than 20-mg/day in the treatment of adults with ADHD. I agree with their conclusions. The OC analysis showed no trend to increasing efficacy with increasing dose. Shire performed an analysis which assigned patients to a dose group that coincided with the final dose that they actually received as opposed to the dose group to which they were assigned. Drs Massie and Podruchny felt that this type of grouping was inappropriate, and I also agree with them on this point. This type of grouping defeats the randomization of this fixed dose trial and essentially transforms it into a flexible dose trial. Flexible dose trials are notoriously poor at providing reliable information on dose response. In the absence of appropriate statistical approaches that could provide evidence of dose response, Dr. Podruchny employed some qualitative views of response and dose data (such as scatter plot views). These also failed to suggest visual trends of improvement with increasing dose.

I therefore agree that Adderall XR appears to be effective in the treatment of ADHD in the adult population [redacted] (b) (4)

Clinical Question #2-*We were unable to find any analyses of ECG abnormalities and changes from baseline to endpoint by dose group in Study 303. ...*

The sponsor provided an adequate response to this question. The sponsor inappropriately used a Bazzet QT correction in their original analysis which suggested QTc prolongation in the drug groups. Adderall XR predictably leads to mean increases in pulse, and QTcB produces a false increase in QTC when pulse increases. Therefore QTcF is a more appropriate correction for this raw QT data. This correction showed that there were slight decreases in QTc from baseline to endpoint in the treatment groups. The decrease in the placebo group was slightly greater than in the drug groups, but there were no actual mean increases in the drug groups.

Dr. Podruchny notes three cases of right bundle branch block in the Adderall XR treated patients and none in the placebo treated patients. Though right bundle branch block occurred twice in the 20-mg group and once in the 40-mg group but not in the placebo group, I am not concerned that this was drug related in this case. RBBB occurs commonly and there was likewise no apparent dose response.

Clinical Question #3- *We were not able to clearly establish the extent of exposure of ADDERALL XR in the studies in the adult population. Your Table 4, Extent of Exposure in Multiple Dose Studies, implies that only 60 patients received ADDERALL XR for 6 months or greater at any dose and that only 19 patients received 60 mg for a period of 6 months or greater. ...*

Shire confirmed that the numbers that they projected for patient exposure in their pre-NDA meeting were not met. Shire stated that since only one study was required instead of two, they did not generate data for as many patients. The final tally of patient exposure in studies 303 and 304 including patient exposures that are included in the patient update are presented in the following table.

Studies 303 and 304 combined extent of exposure				
Duration	Total # of subjects	Exposed to 20mg	Exposed to 40mg	Exposed to 60mg
< 6 months	151	21 (8.4%)	56 (26.1%)	62 (41.6%)
< 12 months	113	12 (4.8%)	27 (12.6%)	37 (24.8%)

Requirements for a critical mass of safety exposure are generally not reduced by lesser requirements for efficacy data. (b) (4) [redacted]

Clinical Question #4 & 5-*As part of the NDA supplement, the FDA's Adverse Event Reporting System was searched for adverse events in association with Adderall products. Among these adverse events were a number of serious events including myocardial infarctions, cerebrovascular accidents, sudden deaths, and non-fatal cardiac arrhythmias. Of particular concern to us is the fact a number of these events occurred in relatively young adults who appeared to have no other explanation of their event....*

DNDP was concerned about several reports of sudden death and serious cardiovascular system adverse events in the AERS database. Among these were cases involving unexpectedly younger patients. DNDP was concerned that even if effective, there might be a suggestion that long term use of stimulants in the adult population might be too great a cardiovascular safety risk to approve it. DNDP therefore consulted ODS during the initial review of supplement 005 with this concern. The ODS consult report is summarized in Dr. Jones' review. She concurs with the ODS evaluation that these cases do not as a group constitute a signal for increased death or serious adverse events in patients taking stimulants within the dose ranges that would be prescribed. This data does not provide evidence that a risk of sudden death, stroke or myocardial infarction exists above the background rate even when compared to age appropriate cohorts.

This is comforting enough that I can recommend that Adderall XR to be approved at 20-mg/day from a safety standpoint. Amphetamine predictably increases pulse and blood pressures and based on new reports from the American Heart Association, this will potentially have some long term effects on cardiovascular risk if blood pressures exceed 115/73. Other psychiatric drugs that are approved for adults increase blood pressure (e.g. venlefaxine) and carry recommendations for monitoring in the PRECAUTIONS section. Such language already exists in Adderall XR labeling. I therefore agree with Dr. Jones that labeling for Adderall XR with respect to hypertension need not be modified.

Both Dr Jones and the ODS consult note that there is an association between underlying structural cardiac abnormalities and pediatric sudden death during Adderall® treatment. Dr. Jones states that because cardiac abnormalities are risk factors for sudden death in themselves, it is difficult to assess the contribution of stimulant therapy when both are present in the same case. She and the ODS consult suggest modifying labeling to reflect these events. I concur.

Dr. Jones also suggests language in the abuse potential warning that includes the association of sudden death, stroke and other serious cardiovascular events with amphetamine abuse. I do not object with this recommendation; however, it is somewhat gratuitous since these types of adverse events are fairly well known to occur in association with amphetamine abuse. I therefore feel that it would not necessarily be required if Shire had a reasonable basis for an objection to it.

Clinical Question #6, Literature Review- *We are concerned that there may be deficiencies in the reporting and tabulation of adverse events presented in the application. These deficiencies can be considered to fall into several categories. …*

Dr Podruchny addressed Shire's response to question #6 and the literature review. I found nothing in these items that required further information from Shire or modifications to labeling.

6.0 Non-US labeling
To my knowledge Adderall XR is not approved in any country for the treatment of adult ADHD.

7.0 Recommendations and Conclusions
I believe that Shire has adequately addressed the Division's clinical questions in their response to approvable letter of February 13, 2003. In my opinion, negotiating the final labeling is the only task that remains to be accomplished prior to taking an approval action for a dose of 20-mg/day in adult ADHD.

Draft labeling is attached to this memo. There are but a few changes from the Division's draft labeling that was issued with the action letter of October 17, 2003. In the attached draft labeling I have retained the recommendation for a maximum dose of 20-mg/day in adults. I have added Dr. Jones suggested language to the black box warning that describes the association of death and serious cardiovascular events with amphetamine abuse. I have also added Dr. Jones suggested language to the WARNINGS section that describes the association of sudden death with structural cardiac defects.

I recommend that the Division approve Adderall XR for the treatment of ADHD in the adult population at a dose of 20-mg/day based on the available data. (b) (4)

I concur with both the ODS consultants and with Dr. Jones that the AERS reports do not provide evidence for a signal for drug related sudden death, stroke, or serious cardiovascular adverse events that is above the background rates for these events. During the initial review of Supplement 005, I had been concerned that if there had been a signal for increased rates of death or serious cardiovascular adverse events in the AERS database, then Adderall XR could not be approved for adult ADHD. ODS and the DNDP safety group have reviewed the available post-marketing data and concluded that there is no such alarming signal. I have added these events to the narrative list of "other events that have been reported with amphetamine use" that follows the adverse event tables. I therefore feel that the Division may take an approval action for Adderall XR in the treatment of adult ADHD once final labeling is negotiated.

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/s/

Paul Andreason
8/3/04 03:29:04 PM
MEDICAL OFFICER

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: October 9, 2003

FROM: Paul J. Andreason, M.D.
Team Leader, Psychiatric Drug Products
Division of Neuropharmacological Drug Products
HFD-120

SUBJECT: Recommendation for Approvable Action with requirements for additional study

TO: File, NDA 21-303
[Note: This memo should be filed with the December 18, 2002 original submission of this NDA.]

1.0 BACKGROUND

Shire pharmaceuticals Development Inc. Submitted supplement 005 (b) (4) under NDA 21-303 on December 18, 2002. This supplement 005 presents data in support of the indication of treatment of Adult Attention Deficit Hyperactive Disorder (AADHD) (b) (4)

Adderall XR is currently approved for the treatment of ADHD in children ages 6-12 years old. It carries a Black Box Warning for risk of amphetamine dependence and abuse and is a Schedule II-non-narcotic. It is contraindicated in advanced arteriosclerosis, symptomatic cardiovascular disease, moderate to severe hypertension, hyperthyroidism, glaucoma and known hypersensitivity or idiosyncrasy to sympathomimetic amines. The PRECAUTIONS section states that patients' blood pressure should be monitored at appropriate intervals, especially patients with hypertension. Most of the contraindications and precautions mentioned in this paragraph bring adult patients to mind even though Adderall XR® is not currently approved for them.

Some estimate that 2-4% of adults have AADHD. Atemoxetine (Strattera®) is the only drug approved for the treatment of AADHD. It is not a scheduled substance, but is available only by prescription. As recently as 1985 Paul Wender, MD, a major researcher in and proponent for codifying the diagnosis of AADHD stated that although the data had convinced him that AADHD was an entity that persisted into adulthood and that stimulants could be helpful, he feared treating adults outside of a research setting with controlled stimulants because of DEA scrutiny. Over the last 15 years it has become increasingly clinically acceptable for psychiatrists to treat AADHD off label with scheduled stimulant drugs, but with great reservation. I believe that it is highly likely that once any scheduled stimulant is approved for the treatment of AADHD that the use of these drugs will significantly increase in the adult population and that prescribing will spread more widely to non-psychiatric physicians.

It is widely accepted and currently labeled that amphetamine is capable of raising blood pressure. It is also widely accepted that adults who can lower their blood pressures will decrease their risks from cardiovascular illness and death. It is unknown what the effect of systematically artificially raising blood pressure may do in the adult population; however, in the light of the recent, highly publicized death of a Major League Baseball pitcher that was attributed to Ephedra and the removal of

phenylpropanolamine from the market, the major and perhaps most controversial concern of the clinical review Teams (DNDP and ODS) is the long term effect of the amphetamine pressor action. I will summarize the data and recommendations on safety of the various Teams, the Chemistry, Statistics and Biopharmaceutics (OCPB) concerns, and finally offer my own recommendations on approvability of Adderall XR for AADHD in this memo.

2.0 CHEMISTRY

Adderall XR is a currently marketed drug, (b) (4) (b) (4) Chemistry recommended an Approval Action on (b) (4) on August 15, 2003.

3.0 PHARMACOLOGY/TOXICOLOGY

Adderall XR is a currently marketed drug. There were no pharm-tox issues under review in this submission.

4.0 BIOPHARMACEUTICS

OCPB recommends approval (b) (4). Kofi Kumi, PhD was the primary OCPB reviewer. OCPB has four action items for the sponsor after reviewing this supplement

(b) (4)

(b) (4)

(b) (4)

5.0 CLINICAL EFFICACY

The primary Clinical Reviewer for both efficacy and safety was Glenn Mannheim, MD. The primary Biometrics and Statistical Reviewer was Tristan Massie.

The sponsor submitted study 381.303 as one pivotal study in support of efficacy. The Division decided that only one positive study was required because AADHD is a disorder that begins in childhood, carries on into adult years, and is expected to respond in the same fashion to treatment as in children.

Study 303 was a 6-week, double blind, randomized, placebo controlled, parallel group study of men and women with AADHD as defined by DSM-IVTR. There were four treatment groups: placebo, and Adderall XR 20, 40, and 60-mg/day. All patients started at 20-mg/day. Patients in the 40 and 60-mg/day groups were titrated up to dose at a rate in 20-mg/week increase. 255 patients were randomized equally among the four groups resulting in 61-66 patients per group. The primary efficacy analysis was a last-observation-carried-forward (LOCF) analysis of the intent-to-treat (ITT) population of the mean change from baseline of the ADHD-RS total score.

Subject disposition is as follows

Disposition of patients in study 303*

	Placebo	Adderall XR 20 mg	Adderall XR 40 mg	Adderall XR 60 mg	Total
Randomized	64	66	64	61	255
Completed	42 (65.6)	47 (71.2)	49 (76.6)	45 (73.8)	183 (71.8)
Primary Reason for discontinuation n (%)					
Adverse Event	1 (1.6)	9 (13.6)	6 (9.4)	8 (13.1)	24 (9.4)
Protocol Violation	1 (1.6)	1 (1.5)	1 (1.6)	0 (0.0)	3 (1.2)
Withdrew consent	4 (6.3)	0 (0.0)	1 (1.6)	1 (1.6)	6 (2.4)
Lost to follow-up	2 (3.1)	4 (6.1)	1 (1.6)	3 (4.9)	10 (3.9)
Lack of Efficacy	14 (21.9)	5 (7.6)	6 (9.4)	4 (6.6)	29 (11.4)

*Extracted from Tristan Massie's review

The results of the analysis of baseline to endpoint change in the total ADHD-RS score is as follows:

ADHD-RS Total Score at Baseline and Endpoint for the ITT Population in Study 303*

		Placebo	**20-mg**	**40-mg**	**60-mg**
Baseline	N	60	64	64	60
	Mean (SD)	33.0 (8.75)	31.1 (9.61)	31.3 (8.13)	32.9 (9.83)
Endpoint	N	60	64	64	60
	Mean (SD)	26.4 (12.24)	18.5 (12.48)	18.4 (11.50)	18.5 (11.68)
	p value	N/A	0.001	<0.001	<0.001

*Extracted from Tristan Massie's review

The efficacy and analysis of study 303 therefore support the claim that Adderall XR is effective in the treatment of AADHD; however, Dr Mannheim raises a question on the appropriateness of the use of the ADHD-RS as a valid and reliable rating scale in measuring clinical progress for the adult population. He points out correctly that this is a scale that was designed for children; however, there are no rating scales for AADHD that have undergone rigorous psychometric evaluation.

The ADHD-RS is a 18-item scale published by DuPaul. Each item is scored on a scale of 0-3. Items 1, 3, 4, and 9 are questions that apply most closely to school behaviors and are not as easily tracked or defined in the adult working life where rules of behavior are not quite so rigid or predictable. On the other hand, the other items can apply directly to adult life and therefore have at least face validity. A possible solution to this apparent problem would be either to delete the items from this scale or redefine the scale for adults. The sponsor chose to leave the scale intact rather than make subjective modifications without validation and reliability data.

A reanalysis of the data without items 1, 3, 4, and 9 revealed that all treatment groups remained statistically significantly improved over placebo on the modified total ADHD-RS score of the remaining variables (20-mg p=0.002; 40-mg, p=0.0007; 60-mg, p=0.0002). I therefore do not agree with Dr. Mannheim that the choice of rating scale was inappropriate. Though it was not tailor made for the adult population, no more appropriate scale was available. The results also hold up to post hoc FDA statistical exploration of subscales that were viewed as appropriate to the adult population.

Conclusions on Efficacy
Adderall XR is effective in the treatment of AADHD (b) (4)

5.1 CLINICAL SAFETY
CARDIOVASCULAR RISK
Which action to take on supplement 005 remains a controversial issue based on safety concerns raised by Dr. Mannheim. His concerns are based on a combination of knowledge of the pressor effects of amphetamine and a collection of cases of deaths and serious cardiovascular adverse events from the post-marketing AERS database. Given Dr. Mannheim's concern, Judy Racoosin, MD Safety Team Leader was notified and she recommended an Office of Drug Safety (ODS) consultation. The primary reviewer for ODS on this consult was Kate Gelperin, MD, MPH. A meeting of the Clinical Review Team, Dr. Racoosin of the DNDP Safety Team, and the ODS Review Team was held on October 7, 2003 to discuss the safety data at hand and possible Division actions. I note that ODS is currently performing a safety evaluation of stimulant therapy (including methylphenidate and amphetamine) and this ODS consult report represents a partial preliminary report on that project.

A search of the AERS safety database was conducted using the following product criteria: Adderall trade name, trade name verbatim(s), “amphetamine”, and “dextroamphetamine”. This search identified a total of 1511 reports, of which 358 were received directly by the FDA, and 1152 were received from the manufacturer. This preliminary count did not include an analysis of duplicate reports. A fatal outcome was reported in 123 cases. A tabular listing of some of these cases follows:

Selected Cases from AERS database*

MedDRA PT	Total Cases	Life-threatening	Fatal
Arrhythmia NOS	20	2	11
Cardiac arrest	22	4	18
Cardiomegaly NOS	8	0	7
Myocardial infarction	18	5	4
Tachycardia NOS	42	2	2
Ventricular tachycardia	5	2	1
Ventricular fibrillation	5	3	2
Chest pain	39	4	3
Death NOS	9	n/a	9
Sudden death	8	n/a	8
Accidental overdose	15	0	7
Cerebrovascular accident	25	1	3
Coma	23	3	11
Convulsions NOS	59	5	5
Grand mal convulsion	19	2	0
Haemorrhagic stroke	1	0	1
Loss of consciousness	9	1	2
Subarachnoid haemorrhage	3	1	2
Syncope	15	0	0
Pulmonary oedema NOS	12	0	11
Circulatory collapse	8	1	6
Hypertension NOS	38	1	2

**Please note that this table may include duplicate reports. Extracted from Dr. Gelperin's ODS review.*

Study 303 is the only source of placebo controlled adult safety data on Adderall XR available to the Agency for review at this time. It is a fixed dose study; however, several patients did not reach the maximum dose that was intended for their treatment group. Though this is an acceptable situation for the efficacy study, it minimizes a potential dose dependent effect. Mean and outlier data from study 303 follows:

Outlier analysis of vital signs in study 303*

Diastolic HTN (>90-mmHg)		Systolic HTN (>160-mmHg)		Tachycardia (>100 bpm)		Bradycardia		Tachypnea (>20-bpm)	
Drug (n=188)	Placebo (n=60)	Drug	Placebo	Drug	Placebo	Drug	Placebo	Drug	Placebo
41 (22 %)	12 (20 %)	4 (2 %)	0	28 (15 %)	5 (8.3 %)	0	1	23 (12 %)	6 (10 %)

*Extracted from Dr Mannheim's review. Adderall treatment groups were not separated by dose.

Mean Changes in Vital Signs in Study 303			
	Placebo	Adderall XR	p-value
Systolic BP (mmHg)	-1.9	1.9	0.007
Diastolic BP (mmHg)	2.1	2.5	0.73
Pulse (bpm)	1.9	5.2	0.01
Weight (lbs)	0.2	-4.5	<0.0001

Adderall XR product labeling is quite clear about risks to patients with cardiovascular disease and hypertension. It is also quite clear that vital signs should be done as a routine matter as a precaution

even in patients with no cardiovascular symptoms or hypertension. It is not contraindicated in patients with mild hypertension though it is contraindicated inpatients with moderate or severe hypertension.

The ODS arrived at the following conclusion in their review:

> Preliminary review of the marketed safety experience with dextroamphetamine products, including Adderall, suggests that potentially important safety issues (e.g., cerebrovascular and cardiovascular serious adverse effects, including fatal myocardial infarction or stroke) need further study and clarification to enable accurate risk assessment and communication (labeling) for the appropriate use of this drug in adults. Additional information about the risks associated with short-term, and especially longer-term therapy in adults, is essential to provide sufficient data to enable enlightened decision-making with regard to the benefit to risk ratio for this product. Factors which may influence risk of adverse effects, such as age, gender, pre-existing disease, need to be further explored. The conduct of well-controlled clinical trials should be considered with appropriate attention to sufficient power and duration of therapy to adequately determine the safety profile of this drug in adults. Attention should be given to potential safety issues in more vulnerable populations such as the elderly, patients with mild or undiagnosed hypertension, and those with potential cardiovascular or cerebrovascular disease.

Dr. Racoosin concurred with this conclusion during the October 7, 2003 meeting with ODS.

EFFECTS ON MOOD

Dr. Mannheim states in his review that Adderall XR has an adverse effect on mood and anxiety both in the short and long term. His conclusion that there is an adverse effect in the short term is based on HAM-A and HAM-D analysis of controlled data from study 303. His conclusion that there is an adverse effect in the long term is based on open-label study 304 spontaneous adverse event report rates compared with the study 303 adverse event report rates.

Short term Effects

Mean changes in HAM-D and HAM-A in study 303 (mean score at baseline-mean score at endpoint)				
HAM_A	Placebo	20-mg	40-mg	60-mg
	-1.7 (6.3-4.6)	-1.6 (6.3-4.7)	0.1* (6.1-6.2)	0.1* (6.0-6.1)
HAM_D				
	-1.2 (4.2-3.0)	-0.7 (3.9-3.2)	0.1* (4.4-4.5)	-0.1* (4.0-3.9)
*$p<0.05$ compared to placebo				

Within the groups, it appears that there is no real change in mood or anxiety except in the placebo and 20-mg groups that actually improve. HAM-D actually numerically improves in all of the treatment groups except for the 40-mg group that has a mean change of 0.1 point. This is clinically insignificant as are the numerical improvements of mean HAM-D scores in the 20 and 60-mg treatment groups. The HAM-A scores are also essentially unchanged in the 40 and 60-mg groups even though there is a decrease in the placebo and 20-mg mean HAM-A score. I conclude that Adderall XR does not cause a

generalizable clinically significant worsening of anxiety or depression in the short term. Individual patients may always have unique experiences.

As part of the standard work-up of this drug, the sponsor should perform an outlier analysis of items 1 and 3 on the HAM-D as an evaluation of suicide induction. The numbers of patients who started with a score on either of these items of 0-2 and who advanced to 3 or 4 should be explored by the sponsor.

Long-term Effects
Whether or not Adderall XR has a clinically significant long-term effect on mood or anxiety remains an open question. The comparisons of incidence of spontaneous adverse reports of anxiety or mood related items are uninformative. Comparing the incidence of spontaneously reported adverse events over different periods of time will always allow for more reports to be collected in the longer term group. Since the reported percentages only reflect the number of patients reporting these events over a period of time, one can not compare the raw counts of events when the collection times differ significantly as they do here. Patients in study 304 (the 6-month open label extension phase) exhibited a dose dependence in the report of nervousness (20 mg: 7.6 %, 40 mg: 8.4 % and 60 mg: 12.9 %). Whether this differs from the short term experience or not is not decipherable from this data.

Conclusions on Safety
Cardiovascular Risk
It is very difficult to assess long term risk based on AERS or open label data for events that have a high background rate. Short term study 303 shows only mild increases in blood pressure. There are clinically significant differences in pulse increase in the short term though.

Though the pressor effects of amphetamine are well known, there were no deaths, or cardiovascular related serious adverse events in study 303. One patient in the Adderall XR treatment groups was discontinued from study 303 due to an elevated blood pressure, but re-enrolled in the long term open label study the same day into study 304. Mean change data showed no difference from placebo in diastolic blood pressure though there was nearly a 4-mmHg mean difference in systolic blood pressure (represented in part by only a 1.9-mmHg increase from the Adderall XR treatment group). Mean pulse differed by 3.3 bpm. Mean values of weight decreased as expected in patients taking amphetamine. The number of outliers for blood pressure was roughly equal between placebo and Adderall XR though tachycardia occurred twice as often with Adderall XR than placebo. Therefore based on this data, the short term effects on the cardiovascular system with Adderall XR treatment in the adult population though measurable did not seem serious.

The long term effect of stimulant treatment in adults is unknown yet concerning. The reports of death and serious cardiovascular pathology in the AERS data, along with the biological plausibility that amphetamine may have had a contribution to these events, leads me to recommend that the Division take an approvable action on supplement 005 pending the performance and analysis of studies like those recommended in the ODS consult. I recommend that both the Sponsor and the Division seek expert cardiology consultation about the design and implementation of studies to explore the long-term cardiovascular risk of amphetamine in adults. The Division may wish to consider accomplishing this through an open advisory committee given the recent public concern with Ephedra, the recent removal of phenylpropanolamine from the market, and the often negative view of stimulants from some groups.

Stimulants remain an effective mainstay in the treatment of childhood ADHD. There is significant off-label use of amphetamine and other stimulants in adults already, but the labeling is sufficiently clear about risks to adults at this time given the current overall prescriber anxiety of using these drugs in adults. The action that I propose (both the lack of suggesting stronger labeling now and the recommendations for studies in the face of proven efficacy) is based on my belief that if and when stimulants are approved for AADHD, the prescribing rates will increase remarkably. This will be due not only to the usual increase seen with commercial marketing, but the FDA official cache of acceptability in using a Schedule II controlled substance in adults for a common condition. This approval will likely remove the currently significant prescriber anxiety of liability attached to its off label use. Primary care providers will likely begin prescribing much more frequently than they do now. I believe that the Agency needs more information before we can make either a reassuring or usefully informative statement in labeling about longer term safety on stimulant use in adults with AADHD.

6.0 WORLD LITERATURE

There is epidemiologic literature which shows an increased risk of cardiovascular events (15 %) and stroke (67 %) based on a 4 to 5 mmHg increase in blood pressure over time[1]. Amphetamines have also been implicated in the etiology of cerebral vasculitis and stroke. It was first described in drug abusers and was though to be related to intravenous administration of methamphetamine[2].

Dr. Mannheim notes that the Sponsor did not submit post-marketing information or a review of the literature with this supplement. He states that twenty-seven (27) photocopied articles were included under the Literature Review Section (Volume 2.13, 8.13.1, References) of this supplement but the Sponsor did not provide a review or discussion of the articles that were referenced and included.

7.0 FOREIGN REGULATORY ACTIONS

I am not aware of any foreign regulatory actions regarding the use of Adderall XR in adult patients with ADHD.

8.0 PSYCHOPHARMACOLOGICAL DRUGS ADVISORY COMMITTEE (PDAC) MEETING

At the filing of this supplement, we decided not to take this NDA to the PDAC. The current dilemma over safety labeling evolved during the review process. The Division may wish to consider a PDAC meeting to discuss the design and importance of the safety studies suggested in this memo.

9.0 DSI INSPECTION

The Good Clinical Practice Branch I & II (HFD-46/47), Division of Scientific Investigations, inspected two (2) investigator sites of high patient enrollment. They were: (No: 112) D. Kelsh, M.D., ET. AL., Vince and Associates Clinical Research, Overland Park, KS and, (No: 124) K. Toups, M.D., ET. AL., Bay Area Research Institute, Walnut Creek, CA. An audit of all subjects' records was conducted and no major compliance issue was noted. It was reported that the source documents and CRF's generally agreed with data listings. The data appeared acceptable.

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[1] Collins R, Peto R, MacMohan S, et al. Epidemiology. Blood pressure, stroke and coronary heart disease. Part 2, short-term reductions in blood pressure: an overview of randomized drug trials in their epidemiological context. Lancet 1990; 335:827-38

[2] Perez JA Jr, Arsura EL, Strategos S. Methamphetamine-related stroke: four cases. J Emerg Med. 1999 May-Jun; 17(3):469-71.

10.0 LABELING AND APPROVABLE LETTER

10.1 Draft of Labeling Attached to Approvable Package

Our proposed draft of labeling is attached to the approvable letter. As noted, we have made changes to the sponsor's draft labeling.

10.2 Foreign Labeling

To my knowledge, Adderall XR is not approved for the treatment of AADHD anywhere at this time.

10.3 Approvable Letter

The approvable letter includes draft labeling and requests for additional safety studies, a literature update, and a regulatory status update.

11.0 CONCLUSIONS AND RECOMMENDATIONS

- I recommend that the Division take an Approvable Action (AE). Final approval would be based on the production of data that can provide reliable evidence of acceptable long-term cardiovascular safety. The short term data is adequately convincing that Adderall XR is effective in treating AADHD, but there is not adequate data to make a reasonable recommendation on longer term safety. I recommend that both the Sponsor and the Division seek expert cardiology consultation about the design and implementation of studies to explore the long-term cardiovascular risk of amphetamine in adults. The Division may wish to consider accomplishing this through an open advisory committee to discuss their design prior to initiating these studies, given the recent public concern with Ephedra, the recent removal of phenylpropanolamine from the market, and the often negative view of stimulants from some groups.
- Listing 12.2 of the safety update indicates abnormal vital signs. The Sponsor should examine whether there is a dose response for those with abnormal vital signs if possible.
- Dr. Mannheim lists several recommendations in his review for items in the action letter. Since completion of his review the Clinical Team met with ODS. Most of Dr. Mannheim's requests are moot in the face of our view that open label data from 304 and short term data from 303 do not address the current concerns over long term cardiovascular safety.
- As part of the standard work-up of many psychotropic drugs, the sponsor should perform an outlier analysis of items 1 and 3 on the HAM-D as an evaluation of suicidality. The numbers of patients who started with a score on either of these items of 0-2 and who advanced to 3 or 4 should be explored and analyzed by the Sponsor.
- (b) (4)
- The sponsor should adopt the following method and specification (b) (4) of Adderall XR.
    - Apparatus: USP Apparatus II (paddle)

- Speed of Rotation 50 rpm
- Media:
  - Stage 1: pH 1.1 dilute HCL for 2 hours (750 mL) at 37 ± 0.5oC
  - Stage 2: pH 6.0 Phosphate buffer for 1 hour (950 mL) at 37 ± 0.5oC
- Specifications:
  - In 2 hours, (b) (4)
  - In 3 hours, (b) (4)

- (b) (4)

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

/s/

Paul Andreason
10/9/03 03:41:00 PM
MEDICAL OFFICER

CLINICAL REVIEW

REVIEW AND EVALUATION OF CLINICAL DATA

Application Information

NDA#:	21-303 /S005, (b) (4)
Sponsor:	Shire Pharmaceuticals Development Inc.
Date Submitted:	December 18,2002 (S 005 for Adult ADHD (b) (4) (b) (4) (b) (4)
PDUFA Due Date:	October 18, 2003 (S005)

Drug Name:

Generic Name:	Amphetamine
Code Name	SLI 381
Trade Name:	Adderall XR

Drug Categorization:

Pharmacological Class:	Stimulant
Proposed Indication:	Adult Attention Deficit Hyperactivity Disorder (ADHD)
Dosage Forms:	20, (b) (4) mg Capsules
Route:	Oral

Review Information

Clinical Reviewers:	Glenn B. Mannheim, M.D.
Completion Date:	September 08, 2003

Table of Contents

Clinical Review for NDA 21-303 (S005, (b) (4)

Executive Summary

I. Recommendations

A. Recommendation on Approvability

I recommend an "approvable" action(s) for the use of Adderall XR in adults (ages 18-76 years) with ADHD, *only for* the purpose(s) of permitting the Sponsor the opportunity of responding to the many issues enumerated within, concerning the safety and efficacy of this drug. I think that this drug has *serious safety signals*, as evidenced by the short-term (303) and open-label studies (304) and the post-marketing AER's, and that the risks resulting from its routine use would largely outweigh any clinical benefits obtained from its routine use. A decision based on the information reviewed to date, would be "non-approvable" with recommendations for a black box warning for current use in pediatric age groups and narcolepsy. (b) (4)

(b) (4)

B. Recommendation on Phase 4 Studies and/or Risk Management Steps

1. A BLACK BOX WARNING is recommended as an interim action based upon the present available information for pediatric use and narcolepsy.

2. Advisory panel(s) to discuss the safety of stimulants with long-term use and another one to discuss the risks associated with the use of Adderall XR in the adult population, and other issues related to approvability.

3. Current exposure duration is inadequate. Long-term studies of several years duration may be needed.

4. A Risk Management Plan needs to be submitted by the Sponsor because of the high abuse potential present in the adult population. Issues relating to rebound and withdrawal need to be assessed.

5. Phase IV studies need to be conducted to characterize the signal seen in Studies 303, 304 and post-marketing AERS, relating to sex or race differences in adverse events.

6. Given how long amphetamine has been used, there is surprisingly limited information regarding metabolism and excretion. Much of this information comes from the literature which suggests that amphetamine are excreted in human via the kidneys. There is also surprisingly little information concerning how the drug is metabolized in humans. Since, concurrent use of Adderall XR is predicted in this population, drug-drug interaction studies for some of the most commonly prescribed drugs in the attended age groups should be performed (e.g. SSRI's, other sympathomimetic(s), cholesterol lowering drugs, anti-hypertensive, etc).

7. Refer to Section X, B (Conclusions and Recommendations/ Recommendations)for further risk management steps.

II. Summary of Clinical Findings

A. Brief Overview of Clinical Program

Shire Laboratories Inc. (the Sponsor) has submitted this supplemental NDA for Adderall XR (SLI381), a once daily extended-release amphetamine product combining the neutral salts of dextroamphetamine and amphetamine, with the dextro isomer of amphetamine saccharate and d,l-amphetamine aspartate monohydrate, for the additional indication of attention deficit hyperactivity disorder (ADHD) in adults, (b) (4) (b) (4) Product labeling is based on that approved for all amphetamine products by the DESI committee in the early 1970's. Adderall and Adderall XR was previously approved for the treatment of ADHD in children, aged 6-12 years, on 02/1996 and 10/2001, respectively. Currently Adderall XR doses is available as 5 mg, 10 mg, 15 mg, 20 mg and 30 mg capsules. The maximum recommended dose in children is 30 mg/day.

In support of safety, efficacy (b) (4) in adult ADHD, Shire has submitted *SLI381.303 (Study 303)*, a 4 week randomized double blind placebo controlled parallel group comparison of three active treatments (20, 40 and 60 mg) to a placebo group. There was a 1-2 weeks titration for the 40 and 60 mg groups, respectively. In this trial, safety was evaluated in 191 Adderall XR treated subjects (20 mg: 66; 40 mg: 64; and 60 mg: 61) and in 64 placebo subjects. Additional supportive safety data was derived from *SL1381.304 (Study 304)*, a 12 month (amended to 24-month), uncontrolled open-label, continuation study for subjects treated in Study 303 (20 to 60 mg/day). Interim report data cut-off dates were at 3 and 10.5 months,

respectively. The safety population for this trial was comprised of 223 subjects distributed among the doses at the last data cut-off (20 mg: 15 %; 40 mg: 42.1 %; and 60 mg: 42.9 %).

In addition, two (2) new, Phase I, pharmacokinetic studies have also been submitted, and three (3) pharmacokinetic studies in healthy adults previously submitted in the original NDA (21-303) are being referenced. The new studies are:

1) *SLI381.108 (Study 108),* which was performed in healthy adults to assess the dose proportionality of single 20 mg (2 x 10 mg), 40 mg (2 x 20 mg), 60 mg (2 x 30 mg) Doses of Adderall XR.

2) (b) (4)

The referenced Phase I, pharmacokinetic studies are:

1) *SLI381.102 (Study 102),* which assessed the bioavailability of a single 20 mg dose of three (3) SLI381 capsule formulations compared to the marketed Adderall IR tablet formulation dosed 10mg b.i.d. (4 hours apart);

2) *SLI381.103 (Study 103),* compared the bioavailability of a 30 mg SLI381capsule in healthy volunteers when administered as an intact capsule following overnight fast, to an intact capsule administered with food, and to an open capsule sprinkled on applesauce;

3) And, *SLI381.105,* in a single period study, assessed the multiple-dose pharmacokinetics of SLI381 30 mg capsules in fasting volunteers.

B. Efficacy

In Study 303, treatment with Adderall XR was statistically superior to placebo on the primary efficacy measure, ADHD-RS total score, in the 20, 40,and 60 mg groups, by ANCOVA analysis, using LOCF (last observation carried forward) with Baseline Total score as the covariate and fixed effects for treatment groups and centers. The 20 mg group was not quite signifi-cant(p=0.058) in the Study Completers population possibly reflecting placebo dropouts.

Results on the Conners' Adult ADHD Rating Scale (CAARS-S:S), a secondary endpoint, used to assess duration of action at 4 hours and 12 hours post dose using an interactive voice response system were not clear, owing to many calls not being made, and insufficient data entry for the ITT patients. In the Observed Cases population, only the 60 mg group was found to be significant at 4 or 12 hours post-dose. Anxiety and depression, as measured by the HAM-A and HAM-D, respectively, improved in the placebo and 20 mg groups, but, worsened in the 40 and 60 mg groups, and was unchanged in the 60 mg group for depression.

The clinical meaning of statistical significance on the ADHD-RS is uncertain to this reviewer, based on the following: 1) lack of demonstrated validity in the ADHD-RS in the adult population; 2) the scale does not appear to have been modified for adults; and 3) no inter-rater, inter center and subject and center reliability studies are apparent. In addition, in this reviewer's opinion, there is diagnostic uncertainty that all the subjects had ADHD. This arises from the Sponsor not have submitted the results of the SCID-I and KBIT; and uncertainty that the ADHD symptoms were *present before 7 years* and that there were no *co-morbid neuro-psychiatric disorders*, explaining the attention difficulties. In this study, the average length of time since ADHD diagnosis was 5.4 (± 8.30) years. In reviewing CRF's of many subjects with adverse event drop-outs, some subjects[1] appear to have been diagnosed with ADHD on the day of entry into the study, and in others[2] the ADHD could have been explained by antecedent head trauma.

C. Safety

Two out of six (2/6) serious adverse events probably related to the use of Adderall XR occurred (suicidal ideation, paranoia, anxiety, bipolar disorder with psychotic symptoms; severe headaches and left upper extremity weakness). Several adverse events were not labeled serious but were potentially of clinical concern, and are described in detail in the ISS.

In study 303 and 304, 12% and 16.6% of subjects discontinued because of AE's. Multiple AE's occurred in individual subjects.

1 Subjects 103-111 was screened and diagnosed with ADHD on 03/13/02. Subject 104-003 was screened and diagnosed with ADHD on 02/20/02. Subject 104-011 was screened and diagnosed with ADHD on 02/27/02. Subject 129-037 was diagnosed on 03/25/02 and screened on 03/25/02; Subject 113-011 was diagnosed on 02/02/02 and screened on 03/25/02; etc.

2 Head trauma-concussion (subject 124-009), head trauma from a MVA (Subject 115-012, head trauma with resulting coma (Subject 124-001).

In study 303, the overall event rate was 84.4 % and 56.3 % in the drug and placebo group, respectively. The most frequently occurring events in Study 303 were dry mouth (drug: 35.1%; placebo: 4.7 %), anorexia (drug: 33%; placebo: 3.1 %), insomnia (drug: 27.2 %; placebo: 12.5 %), headache (drug: 26.2%; placebo: 12.5 %), nervousness (drug: 12.6%; placebo: 12.5 %), and weight loss (drug: 10.5%; placebo: 0 %). Other events occurring more frequently in subjects on drug in Study 303 were: anxiety (drug: 7.9%; placebo: 4.7 %), agitation (drug: 7.9%; placebo: 4.7 %), dizziness (drug: 7.3%; placebo: 0 %), palpitations (drug: 4.2%; placebo: 0 %), tachycardia (drug: 6.3%; placebo: 3.1%), diarrhea (drug: 6.3%; placebo: 0 %) and nausea (drug: 8.4%; placebo: 3.1%).

In Study 304, as of the 01/31/2003 cut-off date, 1022 AE's were reported for 207 (92.8%) subjects[3]. The most frequently occurring events in Study 304 were dry mouth (42.2%), anorexia (30%), insomnia (26.5%), headache (22.4%), nervousness (20.6%), and weight loss (10.3%). Less frequent AE's included anxiety (9.4%), agitation (9%), dizziness (9.4 %), nausea (9.4%), asthenia (8.1 %), depression (6.7 %) and constipation (6.3 %).

Effects on Anxiety and Depression: In the 4 week Study (303), mean symptoms of anxiety (HAM-A) and depression (HAM-D) improved in the placebo and 20 mg groups, but showed statistical worsening in the 40 mg and 60 mg groups [anxiety: p=0.017 and p=0.010; depression: p=0.018 and p=0.049, respectively]. Change in the 60 mg group was minimal [4.0 (2.98) to 3.9 (4.24)]. In Study 304, the open-label extension, HAM-A and HAM-D were not followed, but increased duration of Adderall XR exposure (mean 4.7 mths) resulted in increases in reported AE's for nervousness (12.6 % to 20.6%) and depression (3.1% to 6.7%). The actual percentage of subjects with nervousness may have been greater, since anxiety was coded as a separate adverse event (9.4 %) for a total of 30 % of subjects who developed anxiety-nervousness.

Vital Signs: The Sponsor identified statistically significant group differences between placebo and Adderall XR groups with regard to systolic pressure (drug: 1.9 mmHg; placebo: -1.9 mmHg), pulse rate (drug: 5.2 bpm; placebo: 1.9 bpm) and weight (drug: -4.5 lb; placebo: 0.2 lb). A subsequent analysis of the blood pressure and pulse by week and dose group showed that the 40 mg group showed the largest increases in SBP at week 4 [5.9

3 Adverse events continuing from Study 303 were considered by the Sponsor as baseline medical history. Only new treatment emergent events were recorded as adverse events.

(p=0.000)], largest increases in DBP at week 3 [2.3 (p=0.054)] and largest increases in pulse at week 3 [8.8 (p=0.002)]. No mean changes in pulse occurred in the placebo and 20 mg groups.

ECG: More treatment emergent ECG abnormalities occurred.

Laboratory: Small statistical mean decreases occurred in the eosinophil count and in serum cholesterol, VLDL and triglyceride levels.

Post-Marketing AERS: Select cases were reviewed to identify potential risks associated with use longer than seen with the 4 week efficacy trial (303) and open label follow-up extension. Identified events consisted of seizures, deaths (pediatric-adolescent), deaths (adults), strokes, myocardial infarctions; arrhythmias in adults, not resulting in death; probably arrhythmias in all patients, not resulting in death; arrhythmias in all patients, resulting in death and not resulting in death; cardiomyopathy; ischemic bowel disease; and vasomotor instability.

Twenty-four (24) deaths were identified in patients who had taken Adderall, fifteen (15) with pediatric-adolescent use, and nine (9) with adult use. Mean age at the time of death was 12.6 and 37.3 years in the pediatric–adolescent and adult patients, respectively. Of the pediatric-adolescent deaths, 12/15 were sudden, occurring with therapeutic doses (10/15) at prolonged treatment (40.5 mths in 8/15) and in the context of physical exertion (6/15). An arrhythmia was thought or determined to be the cause of death in 6/15. Concurrent medication use was present in 4/15 patients and was unknown in 5/15 patients. In 6/15 patients there was no other medications. All pediatric-adolescent deaths occurred in males. Of the adult deaths, 4/9 were sudden, occurring with therapeutic dose (4/9); with both short [4/9(3.87 mths)] and long duration of treatment [2/9(36 mths)]; in the context of physical exertion (2/9). No identifiable risk factors were present in 5/9 patients. Concurrent medications use, occurred in 6/9 patients. Sex distribution was 5 male and 4 females. Strokes, ischemic bowel disease and vasomotor instability seemed to occur much more frequently in females compared to males. These adverse events are described in detail in Section VII, E (Integrated Review of Safety/Post-Marketing AERS).

Conclusion(s): There are concerns regarding safety based on the information reviewed to date in study 303 and 304. The impact of

many of these adverse events [e.g. increased depression and anxiety; anorexia (33%), insomnia (27.2 %), headache (26.2%), weight loss (10.5 %)]have not been adequately addressed for the age group(s) studied. For example, increased DBP may be associated with increased risk of stroke and coronary heart disease; or, insomnia may be a major risk factor for depression in the elderly (≥60 years)[4]. Worsening anxiety and depression in this population necessitate the Sponsor performing future drug interaction studies (e.g. SSRI's, anxiolytics, etc).

The interim analysis of Study 304 coupled with the post-marketing AER's suggests that the exposure duration is inadequate. Consideration should be made to wait for the completion of Study 304 at 24 months, and, or, possibly extending it beyond that to 36 months. A BLACK BOX WARNING is recommended as an interim solution based upon the present available information:

"During the marketing of Adderall IR and XR, serious and, or fatal, adverse events have been reported. These adverse events have included stroke, myocardial infarction, cardiac arrhythmia and sudden death in both adults and children. The prescribing physician should consider health risks versus expected benefits."

Warning labels, such as this, may not be able to prevent sudden adverse events occurring with chronic, normal stimulant use, especially when precipitated by physical exertion. An advisory panel is recommended to discuss this and other related issue(s) further.

The present data has deficiencies and inaccuracies which need to be corrected prior to relying on it for accurate labeling.

D. Dosing

Further data needs to be provided by the Sponsor prior to making a final determination regarding the safety of Adderall XR in the adult population. (b) (4) (b) (4) Adderall XR (20 (b) (4) for the long-term treatment of adult ADHD, a chronic condition.

4 Sukying C, Bhokakul V, Udomsubpayakul U. An epidemiological study on insomnia in an elderly Thai population. J Med Assoc Thai. 2003 Apr;86(4):316-24.

E. Special Populations

The short-term, safety and efficacy of Adderall XR in a pediatric population was previously established in the original NDA submission.

The *age* range examined in Study 303 and 304 were 18-76 years (mean: 39.2 yrs). Elder subjects were under-represented in this sample[5] Older subjects (≥ 40 years) were more likely to report AE's than younger subjects. Young subjects (≤ 40 years) appeared more likely to experience anorexia and weight loss than older subjects. Elderly subjects with renal, hepatic or cardiovascular impairment were not studied. The Change in ADHD-RS Total from baseline to endpoint (LOCF) were reasonably similar in the subjects ≤ 40 years and ≥ 40 years of age.

Women showed a higher incidence of headaches (29.5%, men; 37.4%, women), palpitations (2.7% men; 9.1% women), and anorexia (35.6% men; 45.5% women). *Men* showed a higher of nervousness (25.5% men; 18.2% women). A preliminary review of post-marketing AER's showed that females were more likely then men to develop strokes and show vasomotor instability. The Change in ADHD-RS Total from baseline to endpoint (LOCF) by treatment group for males and females were not significantly different.

Non-Caucasian was more likely to experience anorexia, nausea, and tachycardia and less likely to experience constipation and weight loss than *Caucasians*. Limited conclusions can be made since there were only 27 non-caucasians in the sample. A significant treatment effect (ADHD-RS) was seen in both non-Caucasians and Caucasians.

Further studies need to be conducted to evaluate these differences.

5 Age ranges were grouped by a range of 9-11 years, except for those over 50 years who had a range of 26 years.

Clinical Review

I. Introduction and Background

A. Drug Established and Proposed Trade Name, Drug Class, Sponsor's Proposed Indication(s), Dose, Regimens, Age Groups

Shire's proposed [redacted] (b) (4) ADDERALL XR for adults.

Shire's proposed pharmacokinetics is:

Pharmacokinetics

Pharmacokinetic studies of ADDERALL XR® have been conducted in healthy adult and pediatric (6-12 yrs) subjects, and pediatric patients with ADHD. Both ADDERALL® (immediate-release) tablets and

ADDERALL XR® capsules contain d-amphetamine and l-amphetamine salts in the ratio of 3:1. Following administration of ADDERALL® (immediate-release), the peak plasma concentrations occurred in about 3 hours for both d-amphetamine and l-amphetamine.

The time to reach maximum plasma concentration (T_{max}) for ADDERALL XR® is about 7 hours, which is about 4 hours longer compared to ADDERALL® (immediate-release). This is consistent with the extended-release nature of the product.

A single dose of ADDERALL XR® 20 mg capsules provided comparable plasma concentration profiles of both d-amphetamine and l-amphetamine to ADDERALL® (immediate-release) 10 mg bid administered 4 hours apart.

The mean elimination half-lives for d-amphetamine and l-amphetamine in adults are 10 hours and 13 hours, respectively. In children aged 6 to 12 years, the mean elimination half-life is 1 hour shorter for d-amphetamine (9 hours) and 2 hours shorter for l-amphetamine (11 hours). Children had higher systemic exposure to amphetamine (C_{max} and AUC) than adults for a given dose of ADDERALL XR®, which was attributed to the higher dose administered to children on a mg/kg body weight basis compared to adults. Upon dose normalization on a mg/kg basis, children showed 30% less systemic exposure compared to adults.

ADDERALL XR® demonstrates linear pharmacokinetics over the dose range of 20 to 60 mg in adults and 5 to 30 mg in children aged 6 to 12 years. There is no unexpected accumulation at steady state.

Food does not affect the extent of absorption of ADDERALL XR® capsules, but prolongs T_{max} by 2.5 hours (from 5.2 hrs at fasted state to 7.7 hrs after a high-fat meal). Opening the capsule and sprinkling the contents on applesauce results in comparable absorption to the intact capsule taken in the fasted state.

Special Populations

Gender

Systemic exposure to amphetamine was 20-30% higher in women (N=20) than in men (N=20) due to the higher dose administered to women on a mg/kg body weight basis. When the exposure parameters (C_{max} and AUC) were normalized by dose (mg/kg), these differences diminished.

Race
Formal pharmacokinetic studies for race have not been conducted. However, amphetamine pharmacokinetics appeared to be comparable among Caucasians (N=33), Blacks (N=8) and Hispanics (N=10).

Shire's proposed labeling is:

"Adults
A double-blind, randomized, placebo-controlled, parallel-group study was conducted in adults (N=255) who met DSM-IV-TR criteria for ADHD. Patients were randomized to fixed dose treatment groups receiving final doses of 20, 40, or 60 mg of ADDERALL XR® or placebo once daily in the morning for four weeks. (b) (4)

INDICATIONS

ADDERALL XR® is indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD).

The efficacy of ADDERALL XR® in the treatment of ADHD was established on the basis of two controlled trials of children aged 6 to 12, and one controlled trial of adults who met DSM-IV criteria for ADHD (see CLINICAL PHARMACOLOGY), along with extrapolation from the known efficacy of ADDERALL®, the immediate-release formulation of this substance.

A diagnosis of Attention Deficit Hyperactivity Disorder (ADHD; DSM-IV) implies the presence of hyperactive-impulsive or inattentive *symptoms that caused impairment and were present before age 7 years*. The *symptoms must cause clinically significant impairment, e.g., in social, academic, or occupational functioning, and be present in two 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. For the Hyperactive-Impulsive Type, at least 6 of the following symptoms must have persisted for at least 6 months: fidgeting/squirming; leaving seat; inappropriate running/climbing; difficulty with quiet activities; "on the go;" excessive talking; blurting answers; can't wait turn; intrusive. The Combined Type requires both inattentive and hyperactive-impulsive criteria to be met.

Special Diagnostic Considerations: …
Need for Comprehensive Treatment Program: …

Long-Term Use: The effectiveness of ADDERALL XR® for long-term use, i.e., for more than 3 weeks, in children and more than 4 weeks in adults, has not been systematically evaluated in controlled trials. Therefore, the physician who elects to use ADDERALL XR® for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patients.

DOSAGE AND ADMINISTRATION:

Dosage should be individualized according to the therapeutic needs and response of the patient. ADDERALL XR® should be administered at the lowest effective dosage.

Children….

Adults

In adults with ADHD who are either starting treatment for the first time or switching from another medication, (b) (4)

(b) (4)

Patients Currently Using ADDERALL®- Based on bioequivalence data, patients taking divided doses of immediate-release ADDERALL®, for example twice a day, may be switched to ADDERALL XR® at the same total daily dose taken once daily. Titrate at weekly intervals to appropriate efficacy and tolerability as indicated.

Geriatric Use: ADDERALL XR® has not been systematically studied in the geriatric population.

B. State of Armamentarium for Indication(s)

Atomoxetine (Strattera), a selective norepinephrine reuptake inhibitor, was recently approved for the treatment of adult and pediatric ADHD, based on 2 placebo-controlled trials in children, 2 placebo-controlled trials in children and adolescents, and 2 placebo-controlled (10-week) trials in adults meeting DSM-IV criteria for ADHD (assessed by the CAARS in the adults).It is not a stimulant-like drug; hence, there is a lesser risk of abuse potential, rebound and withdrawal than Adderall XR. Comparison of the most commonly observed adverse events in adult subjects treated with Strattera to those treated with Adderall XR; show that they both cause insomnia and nausea more frequently than placebo (2-2.6:1). Adderall XR more frequently caused dry mouth (2 times greater), loss of appetite (3.3 times greater), weight loss (5.5 times greater), dizziness (2.5 times greater), headaches (2.5 times greater), asthenia, urinary tract infections (5 times greater) and diarrhea (vs. constipation with Strattera). Decreased libido, ejaculatory problems, impotence; urinary hesitation, or, retention, or, difficulties in micturition; dysmenorrhea and constipation were more frequently reported as an adverse event in subjects taking atomoxetine (2.5-3:1) than those taking Adderall XR. Strattera treated subjects had mean increases of 5 beats/min (HR), 3 mm Hg systolic and 1 mg Hg diastolic blood compared with placebo. Mean changes in SBP and heart rate between Adderall XR and placebo were 1.9 mmHg and 5.2 bpm. In Adderall XR, the largest mean difference in SBP occurred in the 40 mg group at week 4 [5.9 (p=0.000)] and week 3 for DBP [2.3 (p=0.054). The 40 mg

Adderall XR group also showed the largest increases in heart rate at week 3 [8.8 (p=0.002)].

C. Important Milestones in Product Development

A pre-NDA Meeting took place between HFD-120 and the Sponsor on April 15, 2002. Available minutes from that meeting indicate the following questions from the Sponsor and the Division's response:

1. *Question: Does the agency agree that an efficacy supplement is the appropriate submission to modify the labeling to include the treatment of adults with ADHD?*

   Paraphrased Response: Adult ADHD was an appropriate indication for an efficacy supplement. For diagnostic purposes, it was apparently agreed that a patient's verbal statement about the onset of his or her ADHD symptoms beginning prior to 7 years of age would be accepted. The sponsor stated that most of the subjects in the trials were anticipated to be treatment naïve.

2. *Question: Does the agency agree that study 381.303 (efficacy study) and an interim report of study 381.304 (safety study) will provide adequate safety and efficacy to support a modification of the labeling to include the treatment of adults with ADHD?*

- Response: Shire indicated that the longest duration of exposure for which data will be provided in the initial submission will be 3 months. Further data will be provided in the safety update; the estimate is that there will be 200 subjects exposed for 6 months. There are no firm plans for study 310 at this time, although that trial was mentioned in the briefing booklet.

  Dr. Katz indicated that this would be an acceptable data set, but that if (b) (4) [redacted]. He also suggested that the post marketing data from the narcolepsy patient population may be relevant.

  Dr. Katz also encouraged Shire to determine not only the optimal dose for efficacy but to explore the full range of doses, including an ineffective dose. The possibility of a 10 mg/ day dose was discussed (i.e., the article by Horrigan and Barnhill submitted by the Shire). Dr. Biederman indicated that

he did not believe this dose will be effective since in his clinic adults are typically started on 20 mg/ day.

A question was raised by FDA about the possibility of abuse potential in the adult population. Dr. Biederman said that in his research clinic, drug- seeking behaviors, such as requests for higher doses by adult ADHD patients, were uncommon.

3. *Question: Does the Agency agree that the three pharmacokinetic studies previously conducted with ADDERALL XR under NDA 21-303 in adult volunteers are sufficient and that no additional pharmacokinetic studies will be required to modify the labeling to include the treatment of adults with ADHD? .*

- Response: FDA requested pharmacokinetic data at the 60 mg dose, since linearity has been demonstrated only as far as the 30 mg dose, which may obtained from a literature report or population pharmacokinetic sampling from the clinical trial. Similarly, Shire agreed to search the literature on amphetamine for information on the pharmacokinetics of Adderall in special populations, such as patients with renal or hepatic disease.

4 (b) (4)

- (b) (4)

(b) (4)

5. Additional Points:

- Dr. Jin asked the sponsor to specify their global test for statistical significance, and pointed out that it would be possible to have a positive overall global result but not reach statistical significance on individual pair- wise comparisons for specific doses to placebo. In that case, it would not be appropriate to combine data from different doses even if this yielded a positive result. Also, he noted that the Dunnett's test may not be ideal if the data are not normally distributed and a non- parametric test has to be used.

- FDA preferred to reserve comment on the proposed labeling in the briefing package pending review of the data in its totality.

IND 58, 037 (069), Amendment # 1 (addition of CAARS-S:S, increased study center numbers and excluding subjects with substance abuse), for Study 303 was submitted to the FDA on 01/08/02 and amended on 05/09/02 (080), Amendment # 2. The statistical analysis plan was submitted on 05/10/02 (081).

IND 58, 037 (069), Amendment # 1, for Study 304 was submitted to the FDA on 01/08/02, amended on 05/09/02 (080), Amendment # 2; amended again on 05/16/02 (083), Amendment # 3; and amended again on 08/29/02 (094).

D. Other Relevant Information

Adderall XR is only marketed in the United States. The Sponsor states that an application is pending in Canada for approval of Adderall XR for the treatment of ADHD in children. Adderall XR is currently available in Canada under a compassionate use program entitled Special Access Program (SAP). Applications have not been submitted in other countries.

E. Important Issues with Pharmacologically Related Agents

Sympathomimetic(s) inhibit synaptic reuptake of monoamines, (e.g. norepinephrine) resulting in CNS stimulation with increased attention and elevation of mood, energy, associated with which are increases in heart rate and blood pressure. Drugs included in this class are cocaine, amphetamine, phenyl-

propanolamine and ephedrine. Many of these drugs are associated with hemorrhagic or ischemic stroke secondary to focal arterial vasoconstriction, cerebral vasculitis, or, acute arterial hypertension[6]; or, have been associated with myocardial infarction[7,8]. Recently dietary supplements containing ephedra have also been implicated in myocardial infarctions, cerebrovascular accidents and seizures in persons aged 30 years of younger (50 % of the cases)[9]. Many of these drugs have also been associated with anorexia, weight loss, hypertension, tachycardia, anxiety and insomnia, etc. These adverse events have both been associated with abuse and therapeutic use.

II. Clinically Relevant Findings From Chemistry, Animal Pharmacology and Toxicology, Microbiology, Biopharmaceutics, Statistics and/or Other Consultant Reviews

- A recent review of select post-marketing adverse events identified an apparent increased risk of sudden death, myocardial infarction, arrhythmias and strokes in a young group of patients (deaths: pediatric-adolescent: n=15, 12.6 years; and adults: n=9, 37.33 years) treated with therapeutic doses of Adderall for prolonged duration(40.5 months for 8 pediatric-adolescent deaths)and physical exertion (6/15 pediatric adolescent deaths). Strokes and vasomotor instability were more common in females (3:1).

  The Office of Drug Safety (HFD-430) is presently conducting a review of serious post-marketing adverse events for Adderall IR and XR, and other amphetamines, in order to clarify potential safety concerns (e.g. deaths, strokes, heart attack, seizures, etc.) and to help define potential risks for the population of intended use (Adult ADHD) and current use (pediatric and adolescent ADHD). An interim consult has been submitted and identifies 123 fatal outcomes in 1511 AERS reports for stimulant medications (amphetamine and

6 Bruno A. Cerebrovascular complications of alcohol and sympathomimetic drug abuse. Curr Neurol Neurosci Rep. 2003 Jan;3(1):40-5.

7 Qureshi AI, Suri MF, Guterman LR, Hopkins LN. Cocaine use and the likelihood of nonfatal myocardial infarction and stroke: data from the Third National Health and Nutrition Examination Survey. Circulation. 2001 Jan 30; 103(4):502-6.

8 Costa GM, Pizzi C, Bresciani B, Tumscitz C, Gentile M, Bugiardini R. Acute myocardial infarction caused by amphetamines: a case report and review of the literature. Ital Heart J. 2001 Jun;2(6):478-80.

9 Evidence on the Safety and Effectiveness of Ephedra: Implications for Regulation; US. FDA-White Paper, 2003; http://www.fda.gov/bbs/topics/NEWS/ephedra/whitepaper.html

methylphenidate. "Of the total 123 reports with a fatal outcome, patient age was reported as 6 – 11 years (8 cases), 12 – 16 years (11 cases), 17 – 20 years (5 cases), 21 – 30 years (31 cases), 31 – 40 years (28 cases), 41 – 50 years (19 cases), 51 – 60 years (6 cases), 61 – 70 years (7 cases), and 71 – 80 years (3 cases)[10]."

- The Office of Clinical Pharmacology and Biopharmaceutics/ Division of Pharmaceutical Evaluation I (OCPB/DPE-1) notes in the original NDA (June, 2001) the following relevant to the current review:

  PK (population-children vs. adults): Amphetamine systemic elimination is faster in children than in adults ($t_{1/2}$ is approximately 1 hour shorter for d-amphetamine and 2 hours shorter for 1-amphetamine in children). However, children had higher systemic exposure to amphetamine (C_{max} and AUC) than adults for a given dose of Adderall XR, which was attributed to the higher dose administered to children on an mg/kg body weight basis compared to adults. *When the exposure parameters are normalized by dose (mg/kg), the result shows that children had 30% less in systemic exposure compared to that in adults.*

  PK (population-male vs. female): *The systemic exposure to amphetamine was about 20-30% higher in women than in men*. This difference is mainly attributed to body weight differences between women and men. When the exposure parameters are normalized by dose (mg/kg), the difference was diminished.

  The current review notes:

  In study 108, the dose proportionality study, healthy adult subjects were given a single oral dose of either Adderall XR 2 x 10 mg capsules or Adderall XR 2 x 20 mg capsules or Adderall XR 2 x 30 mg capsules in an open label, randomized, single-dose, three-treatment, and three-period crossover. AUC and C_{max} were linearly proportional to dose in the range from 20 to 60 mg when given as single doses of 2x 10 mg, 2 x 20 mg and 2 x 30 mg.

  (b) (4)

10 Gelperin K. Safety Evaluation of AERS Data (Interim Report). Office of Drug Safety, Division of Drug Risk Evaluation, 09/23/2003.

(b) (4)

(b) (4) Adderall XR 30 mg is an approved dosage strength.

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The reader is referred to the above review(s)[11,12] for further information.

- The Division of Biometrics I (HFD-710) confirmed that Adderall XR 40 mg, and 60 mg groups were significantly better than placebo at endpoint based on the primary efficacy endpoint (ADHD-RS Total score) in the single 4 week trial. The Adderall XR 20 mg to Placebo comparison was not quite significant at the 0.05 level (p=0.058). Placebo completers seem to have done better than placebo dropouts so this analysis may be biased against the Adderall XR 20 mg group.

  The CAARS:S-S ADHD index (one of the secondary endpoints), was used in an attempt to assess the duration of action of Adderall XR. Subjects called in at 4 hours and 12 hours post-dose on Mondays, Wednesdays, and Fridays. The CAARS:S-S analysis are not as clear cut as for several reasons: 1)many of the calls were not made close to the designated times and no time windows were specified in the protocol; 2) 21 ITT patients had insufficient data to be included in this analysis and it is not clear what effect they might have had on the

11 Kumi, KA, ET. AL., Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation I (OCPB/DPE-1), August 04, 2003.

12 Zhao, H, ET. AL., Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation I (OCPB/DPE-1), June 21, 2001.

analysis; and 3) although the treatment groups were superior to placebo at endpoint using the ITT population with the LOCF method, only the 60 mg group was found to be significant at 4 or 12 hours post-dose for the Observed Cases population.

The reader is referred to the above review[13] for further information.

- The Good Clinical Practice Branch I & II (HFD-46/47), Division of Scientific Investigations, inspected two (2) investigator sites of high patient enrollment. They were:

  (No: 112) D. Kelsh, M.D., ET. AL., Vince and Associates Clinical Research, Overland Park, KS

  and, (No: 124) K. Toups, M.D., ET. AL., Bay Area Research Institute, Walnut Creek, CA

  An audit of all subjects' records was conducted and no major compliance issue was noted. It was reported that the source documents and CRF's generally agreed with data listings. The Data appear acceptable.

  The reader is referred to the above review[14] for further information.

III. Human Pharmacokinetics and Pharmacodynamics

A. Pharmacokinetics

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[redacted]

13 Massie T, ET. AL., Statistical Review and Evaluation-Biometrics I (HFD 710)-July 21, 2003.

14 Khin, NA T, ET. AL., Evaluation of Clinical Inspection-Good Clinical Practice Branch I (HFD 46), Division of Scientific Investigations-July 21, 2003.

Protocol No. 381.108 (Study 108): This was an open-label, randomized, single-dose, three-treatment, and three-period crossover study to assess the dose proportionality of single 20, 40, and 60-mg doses of Adderall XR in twelve (12) healthy adult volunteers (age: 32.5 ± 8.2 years; weight: 163.3 ± 27.3 lbs). The result of the study indicate that the AUC and Cmax were dose proportional in the range from 20 to 60 mg when given as a single doses of 2 x 10 mg, 2 x 20 mg and 2 x 30 mg Adderall XR to healthy adult volunteers. There were no statistically significant differences for both d- and l-amphetamine among the 20 mg, 40 mg and 60 mg doses for Tmax or T ½.

The reader is referred to the review from the Office of Clinical Pharmacology and Biopharmaceutics/ Division of Pharmaceutical Evaluation I (OCPB/DPE-1)for further details.

IV. Description of Clinical Data and Sources

A. Overall Data

In support of safety, efficacy (b) (4) in adult ADHD, Shire has submitted *SLI381.303 (Study 303)*, a 4 week randomized double blind placebo controlled parallel group comparison of three active treatments (20, 40 and 60 mg) to a placebo group. There was a 1-2 weeks titration for the 40 and 60 mg groups, respectively. In this trial, safety was evaluated in 191 Adderall XR treated subjects (20 mg: 66; 40 mg: 64; and 60 mg: 61) and in 64 placebo subjects.

Additional supportive safety data was derived from *SL1381.304 (Study 304)*, a 12 month (amended to 24-month), uncontrolled open-label, continuation study for subjects treated in Study 303 (20 to 60 mg/day). Interim report data cut-off dates were at 3 and 10.5 months, respectively. The safety population for this trial was comprised of 223 subjects distributed among the doses at the last data cut-off (20 mg: 15 %; 40 mg: 42.1 %; and 60 mg: 42.9 %).

Post-marketing AERS was reviewed to identify risks associated with the routine use of Adderall and, or, Adderall XR in the intended population.

B. Tables Listing the Clinical Trials

Section XI, D -17of the Appendix, Tables and Lists, provides tables summarizing clinical studies 303, 304, (b) (4) 108, 102, 103 and 105.

C. Postmaketing Experience

No data on, or review of the literature of post-marketing adverse events for ADHD or narcolepsy (as requested in April 15, 2002 meeting) was submitted by the Sponsor. In response to a request by this reviewer, post-marketing information was submitted on 07/11/03. It was inadequate, consisting largely of table listings. The post-marketing AERS database was reviewed to identify potential risks occurring with current off-label use in adults. Literature was reviewed to identify relevant articles relating to safety.

D. Literature Review

Twenty-seven (27) xeroxed articles were included under the Literature Review Section (Volume 2.13, 8.13.1, References) of this NDA. However, the Sponsor failed to provide a review or discussion of the articles, which were referenced and included. An important reference listed in the references (No. 7: Du Paul G et al (1988) ADHD Rating Scale IV: Checklists, Norms, and Clinical Interpretation, New York, NY: Guildford Press) dealing with the normative data for the primary efficacy endpoint was not included, and had to be subsequently requested.

Less Relevant Literature

Many articles were not relevant to this submission, since the instruments or the age groups or the subject were not evaluated in these studies, e.g., the reliability and validity of the SKAMP Rating Scale in a school setting in non-adult ADHD[15]; or, the evaluation of individual subjects in the analog classroom[16]; or, the effects of Adderall on children as assessed in an analog classroom[17,18]; or, the use of or a comparison of Adderall or MPH in children with ADHD[19,20] ; effects of pharmacotherapy

15 Wigal SB, ET. Al. Reliability and validity of the SKAMP rating scale in a laboratory school setting. Psychopharmacol Bull. 1998; 34(1):47-53.

16 Wigal SB, ET. Al. Evaluation of individual subjects in the analog classroom setting: II. Effects of dose of amphetamine (Adderall). Psychopharmacol Bull. 1998; 34(4):833-8.

17 Swanson J, ET. Al. Objective and subjective measures of the pharmacodynamic effects of Adderall in the treatment of children with ADHD in a controlled laboratory classroom setting. Psychopharmacol Bull. 1998; 34(1):55-60.

18 Swanson JM, ET. Al. Analog classroom assessment of Adderall in children with ADHD. J Am Acad Child Adolesc Psychiatry. 1998 May; 37(5):519-26.

19 Pliszka SR, ET. Al. A double-blind, placebo-controlled study of Adderall and methylphenidate in the treatment of attention-deficit/hyperactivity disorder. J Am Acad Child Adolesc Psychiatry. 2000 May; 39(5):619-26.

(predominantly, MPH) and, or, behavior therapy in children with ADHD[21,22]; or, the use of Adderall for OCD[23]; and, or, the MTA Cooperative Group Studies comparing the effects of behavior therapy alone, or, in combination with pharmacotherapy in children with ADHD plus anxiety. The Sponsor's rational in including them in this submission is not apparent to this reviewer.

Relevant Literature

Other literature showed that ADHD occurs in adults with a similar pattern of psychopathology, cognition and psychosocial function to that seen in children suggesting validity to the diagnosis of ADHD in adults[24]. However, adults with ADHD have less prominent gross motor hyperactivity[25, 12] than children with ADHD. Many adults with ADHD have higher rates of antisocial (18-45 %), conduct, oppositional defiant, major depressive, and anxiety disorders[12]. They also have a *greater amount of substance use*, speech and language disorders [10,26]. Marital disruption is increased, socioeconomic status is decreased[2] and there are greater work difficulties[12]. However, it is clear that ADHD is a *chronic condition*.

As a result of the greater co-morbidities present in adults with ADHD, the risk of abuse and the possibility of tolerance or drug refractoriness may be greater in this population[27]. The common

20 Pelham WE, ET. AL. A comparison of Ritalin and Adderall: efficacy and time-course in children with attention-deficit/hyperactivity disorder. Pediatrics. 1999 Apr; 103(4):e43.

21 MTA Cooperative Group. Moderators and mediators of treatment response for children with attention-deficit/hyperactivity disorder: the Multimodal Treatment Study of children with Attention-deficit/hyperactivity disorder. Arch Gen Psychiatry. 1999 Dec; 56(12):1088-96.

22 MTA Cooperative Group. A 14-month randomized clinical trial of treatment strategies for attention-deficit/hyperactivity disorder. The MTA Cooperative Group. Multimodal Treatment Study of Children with ADHD. Arch Gen Psychiatry. 1999 Dec; 56(12):1073-86.

23 Albucher RC, ET. AL. Adderall for obsessive-compulsive disorder. Am J Psychiatry. 2001 May; 158(5):818-9.

24 Biederman J, ET. AL. Patterns of psychiatric comorbidity, cognition, and psychosocial functioning in adults with attention deficit hyperactivity disorder. Am J Psychiatry. 1993 Dec; 150(12):1792-8.

25 Dulcan M. Practice parameters for the assessment and treatment of children, adolescents, and adults with attention-deficit/hyperactivity disorder. American Academy of Child and Adolescent Psychiatry. J Am Acad Child Adolesc Psychiatry. 1997 Oct; 36(10 Suppl):85S-121S.

26 Faraone SV, ET. AL. Attention-deficit/hyperactivity disorder in adults: an overview. Biol Psychiatry. 2000 Jul 1;48(1):9-20.

27 Findling RL, Dogin JW. Psychopharmacology of ADHD: children and adolescents. J Clin Psychiatry. 1998; 59 Suppl 7:42-9.

comorbidity of substance abuse in adult patients with ADHD may be more of a concern than when a medication is administered by parents[2]. However, on the converse side, Biederman ET.AL[28] assessed the risk for substance use disorder (SUD) associated with previous exposure to psychotropic medication in a longitudinal study of boys with ADHD, and found that untreated ADHD was a significant risk factor for substance use disorder in *adolescence*.

The diagnosis of Adult ADHD is dependent upon childhood history of ADHD (to confirm that the symptoms were present *before 7 years*), a history of school problems[12], family history[12], a complete psychiatric evaluation to *exclude other or co-morbid* psychiatric *disorders*, possible neuropsychological testing to evaluate possible sequelae of TBI or a degenerative process, and a careful medical history, etc[2]. Neuropsychological testing shows that adult patients have impaired vigilance (CPT), perceptual motor speed (digit symbol and coding tests), working memory (digit span tests) and response inhibition (Stroop Color Word test)[12].

Several articles dealt with the use of other drugs (desipramine[29], pemoline[30], and methylphenidate[31]) in the treatment of adult ADHD. The average response rate in the treatment of adults ADHD patients is less than for ADHD children (70 % vs. 50 %), and has been thought to reflect insufficient dosing[12]. Spencer's article[21], references an earlier study by Rapoport[32], which points out that normal people may respond to the use of amphetamines, hence, a positive response rate should not be taken as evidence of having the disorder.

28 Biederman J, Wilens T, Mick E, Spencer T, Faraone SV. Pharmacotherapy of attention-deficit/hyperactivity disorder reduces risk for substance use disorder. Pediatrics. 1999 Aug; 104(2):e20.

29 Wilens TE, ET. Al. Six-week, double-blind, placebo-controlled study of desipramine for adult attention deficit hyperactivity disorder. Am J Psychiatry. 1996 Sep; 153(9):1147-53.

30 Wilens TE, ET. Al. Controlled trial of high doses of pemoline for adults with attention-deficit/hyperactivity disorder. J Clin Psychopharmacol. 1999 Jun; 19(3):257-64.

31 Spencer T, ET. Al. A double-blind, crossover comparison of methylphenidate and placebo in adults with childhood-onset attention-deficit hyperactivity disorder. Arch Gen Psychiatry. 1995 Jun; 52(6):434-43.

32 Rapoport JL, Buchsbaum MS, Weingartner H, Zahn TP, Ludlow C, Mikkelsen EJ. Dextroamphetamine. Its cognitive and behavioral effects in normal and hyperactive boys and normal men. Arch Gen Psychiatry. 1980 Aug; 37(8):933-43.

Side effects with stimulant use are discussed for children and adolescents [13] and are said to be dose related. These include: *increased blood pressure and pulse*, anorexia, insomnia, stomach aches, headaches, irritability, tic exacerbation and rare cases of psychosis and leukopenia. Findling[13] notes that more need to be learned about the metabolism of the psycho-stimulants via P450, especially given the combination pharmacotherapy seen in many co-morbid psychiatric disorders.

The sponsor states that they performed a search on Adderall, Adderall XR, dextroamphetamine, amphetamine, humans, *adverse effects and toxicity* from the years *2000-2002*, and identified only three (3) articles[33, 34, 35] pertinent to the treatment of ADHD in adults. One article (Albucher, Et. Al.) is a case report of a 55 year old male with refractory OCD who reported OCD improvement while taking 10-30 mg of Adderall, and non-worsening of pre-existing tics. The second article (Spencer ET. Al.), describes the results of a randomized, double-blind, placebo-controlled, crossover study (3 weeks per treatment) of Adderall in 27 adult ADHD subjects (mean: 38.8 years). Study medication was titrated up to 30 mg twice a day. The total daily dose during week 1 was 20 mg week 2, 40 mg; and week 3, 60 mg. There was a highly significant improvement in ADHD symptoms using the ADHD Rating Scale ($p<.001$, 42 % decrease). Adderall was well tolerated and there were no serious adverse events. The most frequent adverse events were loss of appetite (0.03), agitation (0.05), insomnia (0.06), anxiety (0.18), dry mouth (0.32), and headache (0.56). Six (6) subjects could not remain on the 60 mg dose because of anxiety (n=3), fatigue (n=1), increased obsessive symptoms (n=1) and confusion (n=1). A significant difference was observed in diastolic blood pressure (76 vs. 71 mg Hg, P=0.02). Weight loss decreased an average of 1.8 kg (4 lb, $P <.001$). The third article (Horrigan ET. Al was an open-label, uncontrolled trial using Adderall (10 mg tab) in 24 subjects (12 M, 12 F; mean age: 33.3 years. Thirteen (54 %) of the subjects responded at doses around 10 mg/day after 16 weeks,

33 Albucher RC and Curtis GC. (2001) Adderall for Obsessive-Compulsive Disorder. Am J Psychiatry 158:818-819.

34 Horrigan JP and Barnhill U (2000). Low-Dose Amphetamine Salts and Adult Attention-Deficit/Hyperactivity Disorder. J Clin Psychiatry 61:414-417.

35 Spencer T et al. (2001). Efficacy of a Mixed Amphetamine Salts Compound in Adults with Attention-Deficit/Hyperactivity Disorder. Arch Gen Psychiatry 58:775-782.

as evidenced by changes in the CGI and Copeland(inattention/ distractibility decreased by 41 %) and showed less side-effects. Nine (38 %) of the subjects were poor responders and showed greater side-effects. Overall side-effects for both groups consisted of generalized anxiety (n=5, 21 %), acute anxiety (n=4, 17 %), decreased appetite (n=3, 12 %) and irritability (n=3, 12 %). The most frequent adverse events for both groups were generalized anxiety (n=5, 21 %), acute anxiety (panic; n=4; 17 %), decreased appetite anxiety (n=3, 12 %), and irritability (n=3, 12 %).

A literature search was conducted by the reviewer to identify other literature *relevant to adverse effects and toxicity* for the period identified by the sponsor (2000-2002). In addition, a search and literature review was conducted for the period prior to 2000. This literature is referenced in the safety section of this review.

. The identified literature includes:

- **2000-2002**:

1. Horrigan JP. ET. AL. Adderall, the Atypicals, and Weight Gain. J. Am. Acad. Child Adolesc. Psychiatry, 40:6, pg. 620, June 2001

2. Thomas S., ET. AL. Adderall and Seizures. J. Am. Acad. Child Adolesc. Psychiatry, 41:4, pg. 365, April 2002

3. Stowe CD, ET. AL. 24-Hour Ambulatory Blood Pressure Monitoring in Male Children Receiving Stimulant Therapy. Ann Pharmacother 2002; 36:1142-9.

4. Findling RL, ET. AL. Short-Term Cardiovascular Effects of Methylphenidate and Adderall. J. Am. Acad. Child Adolesc. Psychiatry, 2001, 40 (5): 525-529.

5. Brown JM ET. AL. Effects of amphetamines on mitochondrial function: role of free radicals and oxidative stress. Pharmacology & Therapeutics 99 (2003) 45-53.

- **Prior to 2000:**

- Gracious BL. Atrioventricular nodal re-entrant tachycardia associated with stimulant treatment. J Child Adolesc Psychopharmacol. 1999; 9(2):125-8.

- Perez JA, ET.AL. Methamphetamine-Related Stroke: Four Cases. The Journal of Emergency Medicine, Vol 17 (3), pg. 469-471, 1999.

- Schteinschnaider A, ET. AL. Cerebral Arteritis Following Methylphenidate Use. J Child Neurol 2000; 15: 265-267.

- Trugman JM. Cerebral Arteritis and Oral Methylphenidate. Lancet. 1988 Mar 12; 1(8585):584-5.

- Dirkx, CA, ET. AL. Sonographic Findings in Methamphetamine-Induced Ischemic Colitis. J Clin Ultrasound 26: 479-482, 1998.

V. Clinical Review Methods

A. How the Review was Conducted

The clinical review was divided into two general sections efficacy and safety review. The review of efficacy focused on the individual pivotal study (303). There was no examination of pooled efficacy data. Safety data was examined starting from the integrated summary of safety (ISS). Serious adverse events, and adverse dropouts were reviewed for all studies relating to Adult ADHD (303, 304). Data from the controlled clinical trial (303) and the open label trial (304) were pooled, when appropriate, to explore common and drug related adverse events, treatment related changes in laboratory analyses, changes in ECG and vital signs, and other specific searches. Selective cases of the post-marketing AERS database were reviewed to identify risks associated with short and long-term adult and, or, pediatric-adolescent use. The selected cases included: death, stroke, myocardial infarction, cardiomyopathy, arrhythmias, seizures, ischemic bowel disease and vasomotor instability.

B. Overview of Materials Consulted in Review

The paper submission was used for the entire clinical process. For the most part, the clinical review drew only from materials included in the NDA submission. No data on, or review of the literature of post-marketing adverse events was submitted. A

subsequent request[36] for post-marketing information was submitted to the FDA on 07/11/03, and was inadequate, consisting largely of table listings. An electronic dataset of vital signs was received by the agency on 09/09/03 and analyzed looking weekly changes in vital signs by dose per week of treatment. The post-marketing AERS database was reviewed to identify potential risks occurring with current off-label use in adults. The literature review submitted with this sNDA was also sub-optimal, consisting of many irrelevant articles, failure to include relevant articles relating to safety, and providing limited discussion of the literature included. A literature search and review of relevant articles was done.

C. Overview of Methods Used to Evaluate Data Quality and Integrity

The submission was checked for internal consistency. Fifteen (15) narrative summaries were checked against the table listings to help ensure the accuracy of some of the safety data. Many discrepancies and omissions were identified in many vignettes, as indicated below. In total, they raises concerns about the quality of the data and the appropriateness of labeling based on this information.

Subject 124-009 is described as being ADHD treatment naïve, Review of the CRF's indicating that he was previously treated with Ritalin for 3 years, had a previous concussion, and had tension headaches. Baseline ECG was abnormal (right atrial enlargement). The subject's adverse event of headaches and chest pain could have been viewed differently based on this history. The history of a concussion potentially could impact on the diagnosis of ADHD (excluding other *co-morbid* conditions that could explain the symptoms).

Subject 130-001 had other AE's than described in the narrative which just described decreased appetite and weight loss. These other AE's were intermittent sweating and insomnia. The subject was re-enrolled in Study 304 and again developed intermittent insomnia for which she withdrew from the study.
Subject 124-011 entered the open label portion of the study after withdrawing on 04/10/02 from Study 303 because of elevated BP and tachycardia (152/104, 106). The Sponsor's vignette states that "his pulse and diastolic blood pressure were high but not clinically significant." The subject's blood pressure was

[36] Request: Summary and discussion of post-marketing experiences of Adderall XR and Adderall in adults and differences with post-marketing experiences with children; literature review of dealing with the AE's.

(152/104, 106). His ECG at that time converted to abnormal (sinus rhythm with an arrhythmia, later to moderate voltage criteria for LVH-05/08). The subject also had an 8 lb weight loss which was not included. Exclusionary criteria for this study indicate that subjects should have been excluded if they consistently had a blood pressure greater than 139/89 mg Hg.

Subject 106-009 also developed muscle cramps (primary reason), chills and jitteriness. These AE's were not included in the vignette.

Subject 115-008 is listed as last being in the study on April 5, 2002, while the CRF's indicated April 12, 2002. Her adverse events were dry mouth, nervousness, mild amnesia (forgetfulness) and anorexia. The CRF's indicate that at that time her WBC was 11.8 and her platelet count was 721, 000. The CRF's indicate that there was "poor subject compliance." Her AE's resolved the day, she entered Study 304.The subject was enrolled in Study 304, 7 days earlier (04/05/02) and again terminated from the study on 04/12/02. No work-up for the forgetfulness is apparent. It is unclear why this subject was re-enrolled into the study given the afore-mentioned, poor compliance.

Subject 121-004-No significant discrepancies were identified between the CRF's and the vignette.

Subject 129-020 has contradictory information in the CRF's. The CRF's indicate that no vital signs or ECG's could be done since the subject left the study because of the AE's, yet a physical examination is present.

Subject 103-111, a 76 year old male has insomnia and dry mouth listed as AE's on the vignette. The CRF's indicate that the subject had moderate hypertension on study entry (160/116) considered by the medical monitor to be normal for age, even though it was an exclusionary criteria. Vital signs indicate that the subject's heart rate went up during treatment (60 to 92) at study termination.

Subject 104-011: No great difference were identified between the CRF's and the vignette.
Subject 113-011: The CRF's note muscle aches, an additional AE not previously mentioned.

Subject 106-009: The vignette indicated that the subject developed a headache two days after being titrated to Adderall

XR 60 mg on 03/28/02. This could not have possibly occurred, since the CRF's indicate that that her baseline screen was on 03/26/02 and that she terminated from the study on 04/04/02. According to the protocol, the highest dose that she could have been at, would have been 20 mg, or, possibly 40 mg.

Subject 115-004: The CRF's indicate additional AE's than those reported in the vignette. They were diarrhea, fatigue (not asthenia) and insomnia.

Subject 129-037: The CRF's indicates additional AE's than those reported in the vignette. They were increased energy and racey.

Subject 124-001: The vignette indicates that the subject started to titrate up to 60mg on 02/27/02 and on 03/17/02, when he developed agitation. This is not possible since the CRF's indicate that the subject was screened for the study on 02/12/02. The CRF's also indicate that he had a past history of tinnitus, a previous history of a significant head trauma resulting in the patient being comatose. No further information is present on the word finding difficulties, or that there was a slight increase in diastolic blood pressure at the time of the AE (130/94). The sponsor CRF's indicated that the subject was discharged on (b) (6) The primary reason for discontinuing is listed as agitation (pg. 123). The history of head trauma with coma would impact on the diagnosis of ADHD (excluding other *co-morbid* conditions that could explain the symptoms).

Subject 124-003: The CRF's indicate a past medical history of mild anxiety, tension headaches, diarrhea, seborrhea, and episodic back pain. The subject then developed the following AE's: diarrhea, vasodilatation, hand tremors, moderate speech disorder (stuttering) and difficulty concentrating. Two contradictory ECG reports are present one indicates sinus bradycardia, non-specific intraventricular conduction delay and early repolarization (pg. 2) and another report indicates that it was normal.

Many other inconsistencies were found:

The Sponsor states in the 4 Month Safety Update that: "In a total of 280 participants (12 healthy adults, 20 pediatric patients and 248 adult patients with ADHD) treated with ADDERALL XR in this adult development program, six (6) patients sustained a serious adverse event and *only one, episode of depression, was*

considered related to treatment[37]." Reviewing of Table 16 (Patients Discontinued from Study Medication Because of an Adverse Event, included in the Appendix) provided by the Sponsor indicates that *seven (7) subjects discontinued from Study 304 because of depression.* Similarly, numbers and types of adverse events resulting in subject discontinuation, identified by the Sponsor in the synopsis of Study 303 and 304, do not match the numbers in Table 16 [e.g. insomnia in Study 303 is listed in the synopsis as 10 (5.2 %), but in the table, only 5 cases of insomnia are counted].

On page 6, of the 4 Month Safety Update, the Sponsor states: "As of the cut-off date for this interim report.. Approximately 80% of subjects had at least 3 months of drug exposure; and approximately 27% of subjects had at least 6 months." It is unclear to this reviewer, where the extra 7 % of subjects came from.

In subjects discontinuing because of an adverse event, the terms, anxiety and nervousness probably should have been grouped together as a single adverse event, since, it may inadvertently have the effect of decreasing the magnitude of any observed signal in anxiety-nervousness. In study 303 and 304, there were 3 and 4 (303) and 5 and 4 (304) AE's relating to nervousness and anxiety, respectively, resulting in subject discontinuation.

The Division of Scientific Investigations (DSI) made routine site audits.

D. Were Trials Conducted in Accordance with Accepted Ethical Standards

Trials were generally conducted in accordance with Good Clinical Practice Guidelines (GCP). However, there were exceptions. There were nine (9) patients (103-111, 106-009, 115-008, 121-004, 124-003, 124-006, 124-011,130-001, and 130014), who discontinued study medication" in Study 303, who were subsequently enrolled in Study 304 and discontinued that study because of an adverse event. In Study 303, subject 124-011 developed insomnia, moderate hypertension and tachycardia (152/104, 106) for which he withdrew from study on April 10, 2002. On the same date, he was re-entered into the open-label study, and was still hypertensive at week 2 (142/104) when the subject's ECG has

37 4 Month Safety Update-May 6, 2003; pgs. 6-7

becoming abnormal (sinus rhythm with arrhythmia). The subject terminated from the study on 07/22/02 because of worsening of elevated blood pressure and insomnia.

Subject 104-040 had a prolonged QT at baseline in Study 304, possible exclusionary criteria, and developed increased QT prolongation and depression prior to terminating from the study as a result of the adverse event.

Subject 104-015, in the context of baseline ECG showing a sinus arrhythmia and first degree block in Study 304, possible exclusionary criteria, and developed moderate dizziness prior to terminating from the study as a result of the adverse event.

Subject 113-005 entered study 304 with baseline, elevated CK levels and fibromyalgia and developed a further increase in the CK, associated with which was headache, vasodilitation and on-going HTN (140/100).

Similarly, several subjects with head trauma should probably have been excluded since it could have impacted oh the diagnosis of ADHD (excluding other co-morbid conditions. Refer to Section V. C. (Overview of Methods Used to Evaluate Data Quality and Integrity/Clinical Review Methods).

E. Evaluation of Financial Disclosure

Form 3454, the Certification of Financial Interests and Arrangements of Clinical Investigators, signed by the Sponsor, states the he has “not entered into any financial arrangements with any of the listed clinical investigators whereby the value of compensation to the investigator could be affected by the outcome of the study.” No individual statements were submitted for each of the thirty-eight (38) listed sites. Financial declaration(s) of consultant(s) used were not included, yet, their expert opinions had significant impact on possible interpretation and significance associated with data. This should be provided.

VI. Integrated Review of Efficacy

A. Brief Statement of Conclusions

In Study 303, treatment with Adderall XR was statistically superior to placebo on the primary efficacy measure, ADHD-RS total score, in the 20, 40,and 60 mg groups, by ANCOVA analysis, using LOCF (last observation carried forward) with Baseline Total score as the covariate and fixed effects for treatment groups and centers. The 20 mg group was not quite significant(p=0.058) in the Study Completers population possibly reflecting placebo dropouts.

Results on the Conners' Adult ADHD Rating Scale (CAARS-S:S), a secondary endpoint, used to assess duration of action at 4 hours and 12 hours post dose using an interactive voice response system were not clear, owing to many calls not being made, and insufficient data entry for the ITT patients. In the Observed Cases population, only the 60 mg group was found to be significant at 4 or 12 hours post-dose. Anxiety and depression, as measured by the HAM-A and HAM-D, respectively, improved in the placebo and 20 mg groups, but, worsened in the 40 and 60 mg groups, and was unchanged in the 60 mg group for depression.

The clinical meaning of statistical significance on the ADHD-RS is uncertain to this reviewer, based on the following: 1) it does not appear validated for the intended population; 2) the scale does not appear to have been modified for adults; and 3) no inter-rater, inter center and subject and center reliability studies are apparent. In addition, there is diagnostic uncertainty that all the subjects had ADHD. This arises from the Sponsor not have submitted the results of the SCID-I and KBIT; and uncertainty that the ADHD symptoms were *present before 7 years* and that there were no *co-morbid neuro-psychiatric disorders*, explaining the attention difficulties. In this study, the average length of time since ADHD diagnosis was 5.4 (± 8.30) years. In reviewing CRF's of many subjects with adverse event drop-outs, some subjects[38] appear to have been diagnosed with

38 Subjects 103-111 was screened and diagnosed with ADHD on 03/13/02. Subject 104-003 was screened and diagnosed with ADHD on 02/20/02. Subject 104-011 was screened and diagnosed with ADHD on 02/27/02. Subject 129-037 was diagnosed on 03/25/02 and screened on 03/25/02; Subject 113-011 was diagnosed on 02/02/02 and screened on 03/25/02; etc.

ADHD on the day of entry into the study, and in others[39] the ADHD could have been explained by antecedent head trauma.

B. General Approach to Review of the Efficacy of the Drug

The review of clinical efficacy of Adderall XR in the treatment of ADHD in adults focused on the single, parallel group, randomized, double blind, placebo controlled study which examined the efficacy of 20, 40, and 60 mg Adderall XR compared to placebo in adult ADHD patients over 4 weeks.

C. Detailed Review of Trials by Indication

Study SLI381.303 (303): This study was conducted over the 3.5 month period from 02/06/02-02/24/02 by the investigators/sites identified in the Appendix.

Objective(s):

1. To assess the efficacy and safety of Adderall XR (administered as a daily dose of 20, 40 or 60 mg) compared to placebo in the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in Adults (Primary)

2. To assess the duration of action of Adderall XR using two time periods: 4 hours post dose and 12 hours post-dose, three days a week, for the four weeks of treatment.

39 Head trauma-concussion (subject 124-009), head trauma from a MVA (Subject 115-012, head trauma with resulting coma (Subject 124-001).

Population: Subjects were to be healthy adults, 18 years of age or older, KBIT IQ ≥ 80, with a primary DSM-IV-TR criteria[40] diagnosis of ADHD and HAM-A and HAM-D scores < 17 and < 19, respectively. Subjects with co-morbid psychiatric (psychosis, bipolar disorder, PDD, severe OCD, severe depressive or anxiety disorder) or medical diagnoses (seizure, tics, various heart diseases, untreated hypertension [138/89], heart rates < 50 or > 120 bpm, history of transient ischemic attacks, renal impairment or hyperthyroidism) were to be excluded.

Design: Following a one-week washout of prior ADHD therapy, subjects were randomized to a daily morning dose of one of four treatment groups (1:1:1:1 ratio): 20 mg/day, 40 mg/day, and 60 mg/day of Adderall XR or placebo for 4 weeks. Subjects randomized to 60 mg were titrated to that dose over a 2-week period; and those randomized to a 40 mg dose were titrated to that dose over a 1-week period. There was a telephone follow-up at 30 days post discontinuation of study medication to collect information on new and ongoing adverse events, and to follow-up any adverse event. Concomitant use of the following drugs was prohibited (e.g. clonidine, anticonvulsants, antidepressants, anti-psychotics, MAOI's, amphetamines or pemoline, benzo-diazepines, sedating antihistamines, cardiac and vascular).

The following demographic and baseline characteristics (Table in Appendix) were comparable for the treatment groups [age: 39.2 year average (18-76 years), race, weight, ADHD-RS Total Score). Twenty percent (20 %), more females than males were present in the 60 mg (F: 31, 51.7 %) than in the placebo group (F: 19, 31 %), 15.8 % more than the 20 mg (F: 23, 35.9 %) and 11.1 % more than the 40 mg groups (F: 26, 40.6 %). The mean number of years since the diagnosis of ADHD in the respective groups was also longer in the 60 mg group (7.1 years) compared to the placebo (5), 20 mg (4.6) and 40 mg groups (4.9). Prior stimulant use for amphetamines and methylphenidate was greater in the 20, 40 and 60 mg groups (23.5 %, 26.6 % and 25 %, respectively) than in the more stimulant naïve placebo group (13.3 %).

Assessments: Screening assessments were to include a medical history; psychiatric interview; Structured Clinical Interview-Diagnostic, with Psychotic Screen (SCID-1); physical exam;

40 Diagnosis was established by SCID-I interview at screening by a psychiatrist. The subject had to meet at least 6 of the 9 subtype criteria.

clinical laboratories[41]; ECG; Hamilton Depression Rating Scale (HAM-D); Hamilton Anxiety Scale (HAM-A); and the Kaufman Brief Intelligence test (KBIT). All screening assessments were completed while the subjects were on his or her current ADHD therapy (if any). Subjects had to discontinue all medications at least 7 days prior to randomization at Visit 2.

The primary efficacy measure was the ADHD-Rating Scale (ADHD-RS) total score and the secondary efficacy measures were the Conner's' Adult Rating Scale (CAARS), Clinical Impressions Scale [CGI-Severity (S): baseline; CGI-Change (C) and CGI-Efficacy (E): subsequent visits], HAM-D, HAM-A, Social Adjustment Scale-Self Report (SAS-SR) and the Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q). Safety monitoring assessment included physical examinations, vital signs[42], height (baseline only) and weight, ECG's, clinical laboratories[43] and recording of adverse events.

The ADHD-RS completed by each subject and a clinician, referenced each subject's ADHD symptoms in the prior week. It was completed at baseline; weeks 1, 2, 3 and 4. The CAARS-S was a self-reporting rating collected using an interactive voice response system (IVRS) at screening at lunch and dinner-time on Monday, Wednesday and Friday; baseline; weeks 1, 2, 3 and 4 at 4 and 12 hours post dose on Monday, Wednesday and Friday. The CGI-S and the CGI-E were completed at baseline; weeks 1, 2, 3 and 4; the CGI-C was completed at weeks 1, 2, 3 and 4. The HAM-D, HAM-A, Q-LES-Q, SAS-SR was completed at baseline, weeks 2 and 4.

The schedule of events for the 303 study is included in the Appendix.

Analysis Plan: The primary endpoint was the last post-baseline visit for which a valid ADHD-RS score was obtained. The primary efficacy analysis was the analysis of the ADHD-RS total score at endpoint for the intent-to-treat population. An analysis of covariance (ANCOVA) was performed on the ADHD-RS total score, including treatment and center as fixed effects and the baseline

41 Chemistry, hematology, urinalysis, TSH, CK, fasting lipids, urine drug screen and urine pregnancy test (women of childbearing potential)

42 Vital signs included blood pressure, pulse and respiration, which were obtained after the subject was sitting for 5 minutes.

43 Laboratory studies consisted of hematology, chemistry, urinalysis, CK and lipid panel (fasting).

ADHD-RS total score as a covariate. Dunnett's test was used to compare each active treatment group to placebo. An ANCOVA was also performed on the hyperactivity/impulsivity subscales at end point, to the total scores and subscales at endpoint for the per-protocol (PP0 and study completer (SC) populations, and to the total score and subscales for weeks 1, 2, 3, and 4 for all populations.

Secondary efficacy endpoint included: the ADHD-RS at weeks 1, 2, 3 and 4; the CAARS-S:S obtained at 4 hours and 12 hours post dose during each treatment week and at endpoint; the CGI-S, CGI-C, and CGI-E at all post-baseline visits and at endpoint; the HAM-D, HAM-A, SAS-SR, and Q-LES-Q at weeks 2, 4 and endpoint. End point was defined at the last post-baseline observation for that parameter.

Study Subjects/Patient Disposition: Two hundred and fifty five (255) subjects were randomized to the following treatment groups (placebo: 64; 20 mg: 66; 40 mg: 64; and 60 mg: 61) receiving at least one post-baseline primary efficacy (ADHD-RS) assessment [intent-to treat (ITT) population]. Final daily doses of Adderall XR for each treatment group were: 20 mg [20 mg: 66; 100 %], 40 mg [20 mg: 2, 3.3 %; 40 mg: 58, 90.6 %]; and 60 mg [20 mg: 74 (29 %); 40 mg: 69 (26.7 %); and 60 mg: 49 (19.2 %)]. Of the subjects randomized, 206 (80.8 %) were included in the Per Protocol (PP) population[44] with 183 [71.8 %; placebo: 42; 20 mg: 47; 40 mg: 49; 60 mg: 45) completing the study (SC)] and 72 subjects discontinuing. The ITT group used for efficacy evaluation consisted of 248 subjects, and the safety population consisted of all enrolled subjects.

The most frequent reasons for discontinuation for subjects receiving Adderall XR were adverse events (9.4-13.6 %), while the most frequent reason in the placebo group was lack of efficacy (21.9 %) (See Table in Appendix: Subject Disposition for All Enrolled Subjects). Major protocol violations occurred in 32 (12.5 %) of all subjects with 23 (9 %) of them reflecting noncompliance. Duration of exposure for each of the different treatment groups is indicated in Sponsor's Table 20 copied into the Appendix. It is difficult to interpret this table because many subjects are listed as having been exposed for longer than the 4 week randomized portion of the trial (e.g. the 20 mg group should have 4 weeks of drug exposure, the 40 mg should have 3

44 Per Protocol (PP) Population: subjects were excluded if treatment < 2 weeks, < 80 % compliance rate, or, a major protocol violation.

weeks, and the 60 mg should have 2 weeks). Sponsor reported adverse events most frequently causing treatment discontinuation in the Adderall XR group were insomnia (10, *5.2 %*), anxiety (4, 2.1 %), agitation (3, 1.6 %), and nervousness (3, 1.6 %). Three (3) subjects on drug were terminated due to cardiovascular events (tachycardia, hypertension; chest pain with unclear etiology; rising liver enzymes) [See Table in Appendix: Adverse Events Leading to Termination in > 1 % of All Randomized Subjects]. A review of the Sponsor provided subject vignettes of the subjects, who discontinued, indicates that each subject had multiple adverse events. It is unclear to this reviewer how the Sponsor determined the primary adverse event that resulted in termination. The most common terms reported on the Sponsor's vignettes of those who terminated are indicated in the Appendix. They were: insomnia (13; 6.8 %), nervousness-anxiety (8; 4.2 %), agitation-irritability (8; 4.2 %), anorexia (7; 3.7 %), dry mouth (6, 3.1 %) and headache (5, 2.6 %).

Results: Each of the dose groups were significantly more improved than placebo ($p=0.001$, $p<0.001$ and $p<0.001$ for Adderall XR 20, 40, and 60 mg respectively). The ANCOVA model based estimates of the differences in improvement were –6.61, -7.17, and –7.78 for Adderall XR 20, 40, and 60 mg respectively. A table showing the mean Total ADHD-RS scores for placebo and Adderall XR (20, 40, 60 mg) for the four weeks of the study is included in the Appendix.

All three groups were significantly more improved than placebo after the first week, during which all three groups received 20 mg. While the 40 and 60 mg groups were better than placebo for all subsequent visits, the 20 mg group was not significantly better than placebo for visit 5 or 6($p=0.065$ and $p=0.058$ respectively) in the Study Completers. Since only 65% of the placebo group and 72 % of the 20 mg group completed the study this latter finding may be due to the loss of power associated with dropouts.

This is show graphically in a figure in the Appendix showing the mean ADHD-RS Total score by week for each treatment group.

Per-Protocol Population: The results were similar to those of the ITT population. Dunnett's test yielded statistically significant differences between each Adderall group and placebo ($p<0.001$, $p<0.001$, and $p<0.001$).

Study Completers Population: This consisted of 183 (70 .7 %) subjects who had normal study completion. Dunnett's test yielded statistically significant differences between Adderall 40 mg and placebo (p=0.019) and Adderall 60 mg and placebo (p=0.013) but not between Adderall 20 mg and placebo (p=0.058).

The statistical review notes that there was no dose response trend.

On the Conners' Adult ADHD Rating Scale (CAARS-S:S), a secondary endpoint, used to assess duration of action at 4 hours and 12 hours post dose using an interactive voice response system, the results were not clear. This occurred because many of the calls s were not made close to the designated times and no time windows were specified in the protocol. Second, 21 ITT patients had insufficient data to be included in this analysis and it is not clear what effect they might have had on the analysis. Finally, although the treatment groups were superior to placebo at endpoint using the ITT population with the LOCF method, only the 60 mg group was found to be significant at 4 or 12 hours post-dose for the Observed Cases population.

HAM-A and HAM-D

Mean symptoms of anxiety, as measured by the HAM-A, improved in the placebo [6.3 (3.58) to 4.6 (3.57)] and 20 mg groups [6.3 (3.18) to 4.7 (3.65)] and worsened in the 40 mg [6.2 (3.47) to 6.3 (4.77)] and 60 mg groups [6.0 (3.37) to 6.1 (4.97)] from baseline to endpoint for the ITT population. This difference was statistically significant for the 40mg and 60mg groups (p=0.017 and p=0.010, respectively), but not for the 20 mg group (p=0.924). Please refer to the table in the Appendix.

Mean symptoms of depression, as measured by the HAM-D, improved in the placebo [4.2 (2.85) to 3.0 (2.80)] and 20 mg groups [3.9 (2.78) to3.2 (2.88)] and worsened in the 40 mg [4.4 (2.97) to 4.5 (4.08)] and was essentially unchanged in the 60 mg groups [4.0 (2.98) to 3.9 (4.24)] from baseline to endpoint for the ITT population. This difference was statistically significant for the 40mg and 60mg groups (p=0.018 and p=0.049, respectively), but not for the 20 mg group (p=0.667). Please refer to the table in the Appendix.

Study SL1381.304 (304): This study was conducted from March 08, 2002 with an interim report data cut-off date of January 31, 2003 (10.5) months, and with a planned duration of 24 months. The investigator/sites are identified in the Appendix.

Objectives:

1. To assess the safety of 20 mg, 40 mg, and 60 mg of Adderall XR (administered as a once daily dose) in the treatment of ADHD in adults who participated in Study 303 (Primary);
2. And, to assess long-term efficacy using the ADHD Rating Scale (ADHD-RS) (Secondary).

Population: Only subjects who participated in Study 303 were eligible for participation. Subjects who discontinued from 303 prior to study completion were eligible only if they had completed at least 1 week of double-blind treatment and had no clinically important AE which in the opinion of the investigator would preclude exposure to Adderall XR.

Design: The last visit of the double-blind treatment phase of Study 303 served as the baseline visit for subjects entering the open-label extension. There was no intended interrupted of study treatment between the studies. Visits occurred at Weeks 1, 2, 3, and 4 (± 2 days) to assess the safety and tolerance, and to adjust dose levels if needed. After Week 4, visits occurred 30 days apart (± 7 days) for a planned total of 12 months. Subjects were started on a 20 mg daily dose (2 X 10 mg capsules once daily), and could remain at this dose, or, be titrated up to 40 or 60 mg/day, depending on the Investigator's judgment of optimal treatment. Concomitant use of the following drugs was prohibited (e.g. clonidine, anticonvulsants, antidepressants, anti-psychotics, MAOI's, amphetamines or pemoline, benzodiazepines, sedating antihistamines, cardiac and vascular). Please refer to the Appendix for the Schedule of Assessments.

Two hundred and twenty-three (223) subjects were enrolled into this study. Of the 223 subjects enrolled, 93 (41.7%) discontinued the study early and 130 subjects were ongoing as of July 31, 2002. Two hundred and twenty-one (221) subjects were included in the intent-to-treat population. All 223 subjects were included in the safety population.

Assessments: ADHD Rating Scale (ADHD-RS) was used to measure long-term efficacy, and was collected at baseline and all post-baseline visits. Secondary measures include the Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q), and the Social Adjustment Scale Self Report (SAS-SR), which was collected at baseline, and will be collected at Month 6, and Month 12 (or early termination). Safety monitoring assessment

included physical examinations[45], vital signs[46], and laboratory parameters[47], ECG's[48] and recording of adverse events.

Analysis Plan: The primary outcome was ADHD-RS. In the efficacy and safety analyses, the endpoint for any parameter was defined as the last valid post-baseline observation for that parameter. Subjects were considered to have rolled over from Adderall XR without interruption if the last dose date in Protocol 381.303 was the same as the first dispensing date in this study. Subjects were to begin taking the open-label medication (Adderall XR 20 mg) the following day. The ADHD-RS total score, the Hyperactivity/ Impulsivity subscale, and the Inattentiveness subscale were summarized for the ITT population by visit and rollover from Study 303, and whether the subject rolled over from placebo, Adderall XR without interruption or Adderall XR with interruption. The ADHD-RS total score and each of the subscales were also plotted by visit for all ITT subjects.

Study Subjects/Patient Disposition: Two hundred and twenty-three (223) subjects were enrolled in this study, following participation in Study 303. There were 221 subjects (male: 131, 59.3 %; female: 90, 40.7 %) in the ITT group. Baseline demographics are shown in a Table in the Appendix. As of January 31, 2003, the cut-off date, 116 (52 %) of the subjects were exposed from 4-6 months, 47 (21.1 %) of the subjects were exposed for 7-9 months, and 13 (5.8 %) of the subjects were exposed for 10-12 months. The mean length of drug exposure was 141.1 ± 75.22 days. At month 3, the distribution of subjects (data for 161/223 subjects) among the doses was 19.8 %, 37.2 % and 43.0 % for 20 mg, 40 mg and 60 mg of Adderall XR, respectively. At month 6, the distribution of subjects among the doses was 15.0 %, 42.1 % and 42.9 % for 20 mg, 40 mg and 60 mg of Adderall XR, respectively. Ninety-three (93; 41.7%) subjects terminated from the study. Adverse events were the most frequent reasons for discontinuation (37 subjects). Other reasons for study termination were: withdrew consent (20 subjects), lost to follow-up (11 subjects), protocol violation/non-compliance (12 subjects), lack of efficacy (6 subjects), and other reasons (7

45 Physical Examination (including height and weight): baseline and Month 12 (or early termination)

46 Vital Signs: blood pressure, pulse, and respiration

47 Laboratory: hematology, chemistry, lipids, CK, and urinalysis which were conducted at baseline, Week 2, Week 4, Month 3, Month 6 and Month 12 (or early termination).

48 ECG: baseline, Week 2, Week 4, Month 3, Month 6, and Month 12 (or early termination).

subjects). Protocol deviations occurred in 29 (13.0 %) of the subjects with a non-compliance [less than 80 %] occurring in 14 (6.3 %) of the subjects. The AE's that most frequently caused discontinuation in treatment were insomnia (7 subjects), depression (7 subjects), nervousness (5 subjects) headache (4 subjects), anxiety (4 subjects), hypertension (3 subjects) and weight loss (3 subjects). Ninety-two point eight percent(92.8 %) of all subjects experienced at least one adverse event, described as mild to moderate. In 10.8 % of all subjects, the adverse events were severe. The AE's with the highest incidence were dry mouth (42.2%), anorexia (29.6%), insomnia (26.5%), headache (22.4%), and possibly nervousness (20.6 %). The most frequently reported AEs that caused withdrawal of consent were insomnia (7 subjects), depression (7 subjects), nervousness (5 subjects), headache (4 subjects) and anxiety (4 subjects) and hypertension (3 subjects). Nervousness and dizziness worsened with increasing dose (Refer to Table in Appendix: TEAE's Reported by 5 % of All Subjects). Four (4) serious AE's requiring hospitalization were not drug related (pneumo-encephalocele, cholecystitis, renal calculus and burn) and two (2) were drug related (suicide ideation with psychosis- bipolar disorder, and headache with upper extremity weakness).

Results:
For all subjects, the mean ADHD-RS score at endpoint was 12.2 (±9.95), compared to 20.2 (±12.34) at baseline, for a decrease (improvement) of 8.0 (±12.74). This change was statistically significant (one-sample t-test: $p<0.001$). When the analysis was stratified for previous treatment, the largest improvement was seen in subjects who rolled over from placebo (-13.1±13.83), compared to subjects who rolled over from Adderall XR without interruption (-6.3±11.00) and subjects who rolled over from Adderall XR with interruption (-5.8±17.16).

A one-sample t-test of change from baseline was statistically significant for subjects rolling over from placebo and subjects rolling over from Adderall XR without interruption, but not for subjects rolling over from Adderall XR with interruption ($p<0.001$, $p<0.001$and $p=0.137$, respectively).Please refer to the Table in the Appendix.

The high amount of TEAE's in 91 % of subject's raises concerns about long term safety in this population.

Conclusion (s):
A dose response relation with certain AE's was present (e.g. nervousness and dizziness).

D. Efficacy Conclusions

Adderall XR 40 and 60 mg were statistically superior to placebo on the ADHD-RS Total scores at endpoint. The 20 mg group was not significantly better than placebo for visit 5 or 6 (p=0.065 and p=0.058 respectively). This may reflect the dropouts in the placebo and 20 mg groups. Anxiety and depression improves in the placebo and 20 mg groups, but worsens in the 40 and 60 mg groups, as measured by the HAM-A and HAM-D. In the open label study (304), HAM-A and HAM-D were not done, however, subjects in the 40 and 60 mg group were more nervous (20 mg: 7.6 %, 40 mg: 8.4 % and 60 mg: 12.9 %).

Regulatory Issues

- **ADHD-Rating Scale (ADHD-RS**:

The primary outcome measurement of effectiveness was the ADHD-RS. "The Sponsor states that the rating scale was originally developed to measure the behaviors of children with ADHD (DuPaul[49], 1991, 1998) but was revised for adults by Spencer et al. (1995) and Wilens ET. AL. (1996,1998).

Like the scale for children, the ADHD-RS for adults consists of 18 items designed to reflect current symptomatology of ADHD based on DSM-IV-TR criteria. Each item is scored on a 4-point scale from 0 (reflecting no symptoms) to 3 (reflecting severe symptoms) with total scores ranging from 0 to 54. The 18 items may be grouped into two sub-scales, as shown in the Table below: Hyperactivity/ Impulsivity (Items 1 to 4, 8 to 10, and 17 to 18) and inattentiveness (Items 5 to 7 and 11 to 16)."

Table: ADHD-RS Subscales

Subscale	Item
Hyperactivity/Impulsivity	1. Difficulty Remaining Seated 2. Fidgety 3. Difficulty Playing Quietly 4. Talk Excessively 8. Interrupts or Intrudes 9. Blurts Out Answers 10. Difficulty Waiting Turn

[49] DuPaul GL, ET. AL. ADHD Rating Scale-IV: Checklists, Norms, and Clinical Interpretation. The Guilford Press, NY. 1998.

	17. Often “on the go” or Acts Like “driven by a motor 18. Hyperactivity/Restlessness
Inattentiveness	5. Difficulty Sustaining Attention 6. Difficulty Following Instructions 7. Easily Distracted 11. Loses Things 12. Doesn’t Listen 13. Fails to pay Close Attention to Details 14. Difficulties Organizing 15. Avoidance or Strong Dislike of Mental Tasks 16. Often Forgetful

Comment:

In reviewing the scale, published by DuPaul, it is unclear to this reviewer, how this scale was modified for adults. Items identified (marked in yellow) in the Hyperactivity/ Impulsivity Scale are more relevant to children, and do not seem relevant to adults. However, a reanalysis of the ADHD-RS without items 1, 3, 4 and 9 still shows statistical significance (p=0.0022, 0.0007 and 0.0002, for the 20, 40 and 60 mg groups, respectively). Please refer to Table in the Appendix for ADHD-RS without items 1, 3, 4 and 9.

Normative data for ADHD-RS seems to only be available for children and adolescents (5-18 years). The pediatric scale has an internal consistency reliability of 0.86-0.92 and a 4 week test retest reliability of 0.78-0.86 on the home version. The teacher 4 week test retest reliability for this version is 0.88-0.90. Interrater reliability between parent and teacher is 0.40-0.45. Convergent validity is between 0.35-0.85. There is no identifiable normative data for the adult population. Hence, this reviewer is at odds with the sponsor’s statement (pg. 32, Clinical Study Report) of the appropriateness of this measurement (9.1.4). It states that “.. are standard measurements currently employed in adult ADHD studies. It has norms derived from sample populations, and demonstrates good reliability and validity.”

In this study, the ADHD-RS was completed by subjects with a clinician with reference to their ADHD symptoms during the prior week. It is unclear how inter-rater reliability between subject and rater was achieved. Many of the CRF’s reviewed for the subjects who withdrew because of an adverse event suggest that many were completed by the rater. No reliability data was provided between raters within a center, or, between centers. Without this information it is unclear what these changes mean.

- **Non-Submitted Data:**

Results of the SCID-1 psychiatric interview to exclude co-morbid disorders as MDD, OCD and GAD; and the KBIT (IQ Scale) at screening were not submitted with this NDA making it difficult to further characterize this population.

- **Diagnostic Uncertainty:**

The literature provided by the Sponsor indicates that the diagnose of Adult ADHD is dependent upon a childhood history of ADHD (to confirm that the symptoms were present *before 7 years*), a history of school problems[12], family history[12], a complete psychiatric evaluation to *exclude other or co-morbid* psychiatric *disorders*, possible neuropsychological testing to evaluate possible sequelae of TBI or a degenerative process, and a careful medical history, etc.[2] In the April 14, 2002 meeting between the Agency and the Sponsor, it was agreed that for diagnostic purposes, a patient's verbal statement about the onset of his or her ADHD symptoms beginning prior to 7 years of age would be accepted. This was presumably ascertained by asking the subject if item B of the DSM-IV TR was correct (B. Some hyperactive-impulsive or inattentive symptoms that caused impairment were present before the age of 7 years). In this study, the average length of time since ADHD diagnosis was 5.4 (± 8.30) years. In reviewing CRF's of many subjects with adverse event drop-outs, some subjects[50] were diagnosed with ADHD on the day of entry into the study. This is further complicated by the fact that substance abuse and malingering[51] may be common in adult ADHD. Some subjects may also have had co-morbid conditions that could have explained the ADHD symptoms. Other causes of attention difficulties were present in several subjects in which the CRF's were audited[52].

VII. Integrated Review of Safety

A. Brief Statement of Conclusions

In study 303 and 304, 12% and 16.6% of subjects discontinued

50 Subjects 103-111 was screened and diagnosed with ADHD on 03/13/02. Subject 104-003 was screened and diagnosed with ADHD on 02/20/02. Subject 104-011 was screened and diagnosed with ADHD on 02/27/02. Subject 129-037 was diagnosed on 03/25/02 and screened on 03/25/02; Subject 113-011 was diagnosed on 02/02/02 and screened on 03/25/02; etc.

51 Quinn CA. Detection of malingering in assessment of adult ADHD. Archives of Clinical Neuropsychology 18 (2003) 379–395.

52 Head trauma-concussion (subject 124-009), head trauma from a MVA (Subject 115-012, head trauma with resulting coma (Subject 124-001).

because of AE's. Multiple AE's occurred in individual subjects. In study 303, the overall event rate was 84.4 % and 56.3 % in the drug and placebo group, respectively. The most frequently occurring events in Study 303 were dry mouth (drug: 35.1%; placebo: 4.7 %), anorexia (drug: 33%; placebo: 3.1 %), insomnia (drug: 27.2 %; placebo: 12.5 %), headache (drug: 26.2%; placebo: 12.5 %), nervousness (drug: 12.6%; placebo: 12.5 %), and weight loss (drug: 10.5%; placebo: 0 %). Other events occurring more frequently in subjects on drug in Study 303 were: anxiety (drug: 7.9%; placebo: 4.7 %), agitation (drug: 7.9%; placebo: 4.7 %), dizziness (drug: 7.3%; placebo: 0 %), palpitations (drug: 4.2%; placebo: 0 %), tachycardia (drug: 6.3%; placebo: 3.1%), diarrhea (drug: 6.3%; placebo: 0 %) and nausea (drug: 8.4%; placebo: 3.1%).

In Study 304, as of the 01/31/2003 cut-off date, 1022 AE's were reported for 207 (92.8%) subjects[53]. The most frequently occurring events in Study 304 were dry mouth (42.2%), anorexia (30%), insomnia (26.5%), headache (22.4%), nervousness (20.6%), and weight loss (10.3%). Less frequent AE's included anxiety (9.4%), agitation (9%), dizziness (9.4 %), nausea (9.4%), asthenia (8.1 %), depression (6.7 %) and constipation (6.3 %).

Effects on Anxiety and Depression: In the 4 week Study (303), mean symptoms of anxiety (HAM-A) and depression (HAM-D) improved in the placebo and 20 mg groups, but showed statistical worsening in the 40 mg and 60 mg groups [anxiety: p=0.017 and p=0.010; depression: p=0.018 and p=0.049, respectively]. Change in the 60 mg group was minimal [4.0 (2.98) to 3.9 (4.24)]. In Study 304, the open-label extension, HAM-A and HAM-D were not followed, but increased duration of Adderall XR exposure (mean 4.7 mths) resulted in increases in reported AE's for nervousness (12.6 % to 20.6%) and depression (3.1% to 6.7%).

Vital Signs: The Sponsor identified statistically significant group differences between placebo and Adderall XR groups with regard to systolic pressure (drug: 1.9 mmHg; placebo: -1.9 mmHg), pulse rate (drug: 5.2 bpm; placebo: 1.9 bpm) and weight (drug: -4.5 lb; placebo: 0.2 lb). A subsequent analysis of the blood pressure and pulse by week and dose group showed that the 40 mg group showed the largest increases in SBP at week 4 [5.9 (p=0.000)], largest increases in DBP at week 3 [2.3 (p=0.054)] and largest increases in pulse at week 3 [8.8 (p=0.002)]. No

53 Adverse events continuing from Study 303 were considered by the Sponsor as baseline medical history. Only new treatment emergent events were recorded as adverse events.

mean changes in pulse occurred in the placebo and 20 mg groups.

ECG: More treatment emergent ECG abnormalities occurred.

Demographic Adverse Event Interaction Studies: Drug-demographic and drug adverse event interactions studies showed gender and age differences in the type and incidence of adverse events. Older subjects (≥ 40 years) were more likely to report AE's than younger subjects. Young subjects (≤ 40 years) appeared more likely to experience. Women showed a higher incidence of headaches (29.5%, men; 37.4%, women), palpitations (2.7% men; 9.1% women), and anorexia (35.6% men; 45.5% women). Men showed a higher of nervousness (25.5% men; 18.2% women). A preliminary review of post-marketing AER's showed that females were more likely then men to develop strokes and show vasomotor instability.

Laboratory: Small statistical mean decreases occurred in the eosinophil count and in serum cholesterol, VLDL and triglyceride levels.

B. Description of Patient Exposure

The integrated summary of safety submitted by the Sponsor consisted of 280 subjects in 4 clinical trials:

- Study 303, the pivotal trial, consisted of 191 treated with Adderall XR (20 mg: 73, 40 mg: 61, 60 mg: 57);
- Study 304, the open-label, extension trial, consisted of an additional 57 subjects, previously treated with placebo and 166 previously treated with Adderall XR [total:223];
- Study 108, the single dose proportionality, cross-over study consisted of 12 adults;
- And, Study 107, the single dose, bioequivalence cross-over study, consisted of 20 children.

The referenced studies were *not* included in the safety data base. They were:

- Study 102, the single dose bioavailability study in 20 adults;
- Study 103, the single dose bioavailability study in 21 adults;
- And, Study 105, the multiple dose pharmacokinetics study in 20 adults.

Of the 191 subjects in Study 303, all were treated initially with 20 mg/day, of which,118 were titrated to 40 mg and from that group, 57 were titrated to 60 mg. Therefore, duration of

exposure to a particular dose varied. In Study 304, subjects were started 20 mg/day regardless of the dose received in Study 303, and dose titration was at the discretion of the investigator and depended on response to treatment and tolerability. The maximum allowable daily dose was 60 mg. The mean duration of exposure regardless of dose was 141.1 (± 75.22) days (approx. 4.7 mths). For the two (2) studies, 189 subjects (76.2 %) were exposed from 3-6 months. The extent of exposure of the subjects in Studies 303 and 304 are shown in a table in the Appendix.

C. Methods and Specific Findings of Safety Review

Deaths, Serious Adverse Events, Other Significant Adverse Events

No subject died during clinical study 303 and 304. In study 304, there were six (6) serious adverse events (non-fatal)resulting in hospitalization, of which two (2) relate to Adderall XR use(subject 102-021, identified by the Sponsor; subject 115-012, identified by this reviewer). The Sponsor states that five (5) SAE's have resolved and one (1) [accidental injury-burn] remains unresolved. Twenty three (23, 12 %) of the subjects treated with Adderall XR and one (1, 1.6 %) treated with placebo discontinued because of AE's in Study 303, and 34 additional adverse events to the 6 serious AE's, resulted in discontinuation in Study 304.

Serious Adverse Events: The six (6) subjects who had serious adverse events in Study 304 were subjects 102-015, 102-021, 108-005, 104-038, 112-019 and 115-012 (Refer to Table in Appendix). The Sponsor deemed that only subject 102-021 adverse event was related to study drug. Vignettes for the serious adverse events for subjects 102-021 and 115-012 follows, with the remaining serious adverse events (102-015, 108-005, 104-038, 112-019) being located in the Appendix.

Adderall XR 20 mg (n=3)

Subject 102-021, a 38-year old, White male received Adderall XR 20 mg as per blinded protocol from April 9 to May 8, 2002, totaling 30 days for ADHD. He started open-label study drug on May 9, 2002, initially receiving Adderall XR 20 mg, and was up-titrated to 40 mg on 14 May 2002 and to 60mg on May 21, 2002 for increased efficacy. On August 14, 2002, he demonstrated signs of delusional thinking and flight of ideas that required down-titration of the trial medication to 20 mg on August 16, 2002. The symptoms persisted, and the trial medication was permanently discontinued on August 19, 2002. These symptoms were reported as adverse events prior to the patient experiencing the SAE initially reported as 'Suicidal Ideation'.

On (b) (6) the subject called 911 because he was fearful that it was "judgment day", and was concerned whether he was going to go to heaven or hell. He also felt the government was headed by God and the devil, and was teeming with conspiracies. He was then transferred to the outpatient department accompanied by the police. During the initial interview, he admitted to increased paranoia, anxiety, and bizarre thoughts over the preceding several months, and stated that he also considered suicide in an attempt to keep his family from being killed. During the interview, the subject was observed as being cooperative but somewhat hyperverbal. His mood and affect were elated, he was religiously preoccupied and his thoughts were disorganized. He complained of poor sleep, poor concentration and poor memory. His eye contact was poor and he was slow to respond to questions. He was hospitalized for treatment of these symptoms with lorazepam, haloperidol and olanzapine at 10 mg QHS. Laboratory findings included a total T4 of 5.3ug/dL (4.5-12.0), T_3 uptake of 43% (30-40), and TSH of 11.27 mlU/ml (0.49-4.67) for which he was initiated on levothyroxine 0.25 mg followed by levothyroxine 0.15 mg daily. The patient had a positive drug screen for barbiturates on 3 September 2002. The patient stopped the study drug at the advice of the principal investigator on 19 August 2002.

On September 5, he remained delusional, restless, and was having difficulty sleeping, thus he was medicated with haloperidol, lorazepam, and 1 mg of benztropine. (b) (6) he was showing improvement, was devoid of delusional thinking, his affect was somewhat brighter, and he was less religiously preoccupied. His TSH had increased further to 17.92 mIU/mL. He was cleared medically for discharge, and was sent home in the accompaniment of his wife on the following medications: levothyroxine 0.150 mg QD and olanzapine 15 mg OHS. According to the discharge summary, the final diagnosis for Axis I was 'bipolar disorder, currently manic with psychotic symptoms. Post-discharge planning included follow-up with counseling, medication management, and community resources.

An outpatient psychiatric follow-up was conducted on September 12, 2002. When compare to his condition at discharge, the subject was less religiously preoccupied, denied any psychosis, suicidal or homicidal ideations. He had decreased the olanzapine to 5 mg daily due to increased anxiety and insomnia. A diagnosis of bi-polar/ hypomanic disorder was established, and olanzapine was increased to 7.5 mg and divalproxex sodium started at 1000 mg OHS.

Past medical history included: hypothyroidism, insomnia and a twenty-two day episode of paranoia in January 1992. Concurrent medications include levothyroxine sodium, nicotine patch and diphenhydramine/acetaminophen.

On August 19, 2002, the Principal Investigator determined that the event was related to the study drug, and recommended permanently discontinuing it. The subject was withdrawn from the trial due to the adverse events of delusional thinking and flight of ideas.

Subject 115-012[54]**,** a 35 year-old Caucasian female, received open-label Adderall XR 20 mg QD from May 2 to August 8, 2002 (totaling 100 days). On September 9, 2002 the subject contacted the study personnel and informed them she had been hospitalized from (b) (6) and that the study medication was discontinued at that time. According to the patient she complained of severe headaches on August 5 & 6, 2002 and went to the ER where she was referred to a neurologist. (b) (6) (b) (6) the neurologist sent her to the hospital for further testing due to the severe headaches and left upper extremity weakness. All test results were unremarkable, she had a lumbar puncture which was traumatic (elevated WBC's = 150/CUMM and RBC's = 49750/CuMM). She developed a postural component to the headaches which required treatment with a blood patch and Topiramate. Her headaches improved and were well controlled on oral analgesics; she was discharged (b) (6). The headaches continued of moderate intensity until September 7, 2002. Of note the patient had been involved in a MVA in January 2002. The investigator initially determined the event to be 'possibly' related but reevaluated it and determined it to be 'not related'. He determined that the etiology of the headaches was possibly related to the MVA.

Note: A request was made to the Sponsor on 08/19/2003 to provide available medical records hospital discharge summary for subject 115-012 and was received by the agency on 08/22/2003. The Sponsor's vignette is above. The history abstracted from the medical records received is below.

54 A request for the hospital records of this subject was made to the Sponsor on 08/19/2003 and was subsequently received by the Agency. As a result of lateness in the review cycle, it has not been reviewed with the rest of these materials.

Records Reviewed: The subject is a 35 year old female who was involved in a motor vehicle accident in January, 2002, the severity of the accident being uncertain, but, did complain of multiple aches and pains; and intermittent, left side headaches; which were present from the time of the accident. She was on Adderall XR 20 mg QD. She presented with a 4 day history of worsening headaches, left upper extremity weakness and worsening left upper extremity paresthesia and numbness. The subject was hospitalized from [redacted] (b) (6). Admitting vitals signs included a blood pressure of 147/86 and a pulse of 106. The historian taking the admitting notes states an uncertainty as to whether the left upper extremity weakness was related to the motor vehicle accident, or, was new. He notes that a review of old medical records indicated that no there was no previously documented left upper extremity deficit. The subject was described as "a poor historian who was unable to decipher the exact chronicity of her complaints." During her hospitalization, the following work-up was done which was largely negative: a CT (-) cervical spine, CT (-) brain, chest x-ray, carotid doppler, traumatic lumbar puncture, MRI brain (+/-), MRI angiography of neck and brain, EEG, echocardiogram, ECG, and some blood studies. The subject was treated empirically for CNS infection, pending the cultures. She was also treated for presumptive migraines with dilaudid, phenergan and Imitrex showing little clinical benefit. She was started on Topamax 25 mg qhs for presumptive post-traumatic headaches. A post-LP headache was treated with a blood patch. No neurological examination was apparent in the information reviewed despite a reference to neurology having been consulted. She was discharged on Adderall XR 20 mg, Vioxx 25 mg QD, Darvocet PRN, and Topamax. A progress note written after the hospitalization (09/19/02) in the Clinical Study Notes, indicates that subject reported "seeing flashes of light, experiencing foul smells and having a bad taste in the month for unknown days prior to Visit 8 (08/01/02)", and experienced "a severe headache (08/05/02)". The initial SAE on the CRF is a seizure, which is crossed out, and listed as a non-specific headache. The subject was discontinued from the trial.

Subject 112-019 (see Appendix)

Adderall XR 40 mg (n=1)
Subject 104-038 (see Appendix)

Adderall XR 60 mg (n=2)
Subject 102-015 (see Appendix)

Subject 108-005 (see Appendix)

The Sponsor deemed that only subject 102-021 adverse event was related to study drug.

Comment:
This reviewer is not in agreement with that conclusion. Subject 115-012, classified by the sponsor as being a headache, and being unrelated, had a history that was concerning. This subject was on 20 mg of drug for 100 days when she complained of severe headaches and was found to have left upper extremity weakness which apparently resolved following a brief hospitalization. The sponsor related this to a prior motor vehicle accident, hence, stated that it was not related.

Review of the medical records received from the Sponsor indicates that the subject presented with tachycardia and a week history of flashing lights, foul smells, worsening headaches, and a 4 day history of left upper extremity weakness, paresthesias and numbness. This sounds like a TIA or a complex partial seizure. Insufficient information is available on the severity of the motor vehicle accident to determine its role. The Sponsor had enough information to determine that the patient has had an acute neurological event, some of which, was not present before. Important information was not included by the Sponsor (4 day history related to the left upper extremity paresthesias and numbness with left upper extremity weakness). It is unclear how the Sponsor made the determination that this serious AE was unrelated to drug. Given, the post-marketing observations of stroke and seizures associated with the use of Adderall, this raises serious concerns. If not provided with the last submission, copies of all consults, and, or hospital records, which the Sponsor has relating to this patient should be provided. This case should be looked at further by DSI.

Adverse Events Leading to Discontinuation

Study 303: Twenty three (23, 12 %) of the subjects treated with Adderall XR and one (1, 1.6 %) treated with placebo in Study 303 discontinued because of AE's. Several of them had multiple AE's. Adverse events most frequently causing treatment discontinuation in the Adderall XR group were insomnia (13; 6.8 %), nervousness-

anxiety (8; 4.2 %), agitation-irritability (8; 4.2 %), anorexia (7; 3.7 %), dry mouth (6, 3.1 %) and headache (5, 2.6 %)[55].

Vignettes for subjects who discontinued because of an adverse event in Study 303 are included in the Appendix. The vignettes are as provided by the Sponsor with this submission. The areas marked in yellow reflect the different adverse events identified by this reviewer for each of the subjects. CRF's were audited[56] and deficiencies were identified in 13/15 subject audited cases (86 %). Further details are given in Section V, C (Clinical Review Methods/ Overview of Methods Used to Evaluate Data Quality and Integrity).

Comments: Common adverse events for many of these subjects were insomnia, anxiety, anorexia, weight loss, irritability, agitation, cold extremities and dizziness. A few subjects (124-011, 129-020, 104-011*) developed moderate tachycardia (106 bpm) and one (124-011) developed moderate hypertension (152/104). Insufficient information was present in all cases to judge the severity. Headaches occurred in several subjects (115-004, 106-009,121-004*) but were poorly characterized and not reported in the context of vitals signs and prior medical history, hence, there significance is difficult to determine.

Several adverse events could *potentially be of concern*. They were the presence of *mild amnesia or forgetfulness* (115-008), of a *moderate speech disorder (stuttering) with a worsening of concentration and tremors* (124-003), and *of foggy and abnormal thinking* (116-005). The nature of these events is uncertain and could reflect anything from transient ischemia, seizure, worsening anxiety, or other things. *Chest pain with headaches* (124-009*) and *mild dyspnea with cold hands* (124-006) are also potentially concerning, but insufficient information is provided on vital sign or ECG changes to adequately characterize.

Study 304: The Sponsor states that thirty seven (37; 16.6 %)of the subjects discontinued from study 304 because of AEs, several because of multiple AEs. The most frequently reported AEs leading to discontinuation were insomnia (7 subjects), depression (7 subjects), nervousness (5 subjects), headache (4 subjects) and anxiety(4 subjects).

55 These numbers are based on review of the vignettes. The reasons reported by the Sponsor reported were insomnia (10, 5.2 %), anxiety (4, 2.1 %), agitation (3, 1.6 %), and nervousness (3, 1.6 %).

56 * Denotes that CRF's were audited.

Comment:
The narratives submitted by the Sponsor indicate a higher number of subjects (40, 17.9 % compared to 37) discontinued from the trial.

The Sponsor relates the higher AE's leading to discontinuation in the study 304(16.6%)than study 303 (12 %) to the fact that "there were nine (9) patients (103-111, 106-009, 115-008, 121-004, 124-003, 124-006, 124-011,130-001, and 130014), who discontinued study medication" in Study 303, who were subsequently enrolled in Study 304 and whom "subsequently discontinued study medication in that study as well because of an adverse event" (see Table 16 in the Appendix). Review of some of the CRF's for these adverse events raises questions regarding GCP, and should, in the opinion of this reviewer, be re-evaluated by DSI. For example, subject 124-011 developed insomnia, moderate hypertension and tachycardia (152/104, 106) for which he withdrew from study on April 10, 2002. On the same date, he was re-entered into the open-label study, and was still hypertensive at week 2 (142/104) when the subject's ECG became abnormal ("sinus rhythm with arrhythmia"). The subject terminated from the study on 07/22/02 because of worsening of elevated blood pressure and insomnia. Please refer to Section V, D (Clinical Review Methods/ Were Trials Conducted in Accordance with Accepted Ethical Standards).

Comments (1): Common adverse events experienced by many of the subjects who discontinued from Study 304 were agitation, anxiety, nervousness, insomnia, anorexia, weight loss and dry mouth. It was not clear to this reviewer what the distinction was, if any, between those who developed anxiety and those who developed nervousness.

Several subjects (130-001, 130-014, 113-010, 128-005) developed palpitations, of which two (2) were associated with *tachycardia* (128-005, 116-007). No actual vital signs or changes in vital signs or ECG's were provided in these narratives to judge the significance of these events. Worsening of baseline *hypertension* occurred in two (2) subjects (124-011*,117-011) but again no actual vital signs or ECG's were provided in the context of the history to judge the clinical severity and, or, significance. One subject (121-004) developed *chest pain with weakness* (asthenia), but no vital signs and ECG's were again contextually provided to determine clinical significance. Another subject (102-012) had *pain radiating to the left arm* and *bilateral hand*

numbness, but no follow-up contextual ECG's, vital signs, or, laboratory studies were provided to determine the clinical significance. Another subject (104-015) developed moderate *dizziness* in the context of a baseline ECG showing a *sinus arrhythmia* and *first degree block*. No follow-up ECG or vital signs were reported to determine the significance of this event. However, it is of concern for several reasons. It is unclear if this subject developed this event in Study 303. Another subject (104-040) developed *prolonging of a baseline, prolonged QT syndrome and depression*. No vital sings or ECG's are again, contextually given, to determine the significance of this event.

Weight loss was reported in several subjects (126-004, 130-001, 130-008, 124-003, 116-007) and as being severe in one (126-004), but information on weight loss (16 lb) was provided for only one subject (116-007).

Headaches occurred in several subjects (117-004, 106-009, 112-024, 129-031) but are poorly characterized and not reported in the context of vitals signs and prior medical history, hence, there significance is difficult to determine. *Body aches or myalgia* occurred in five(5) subjects (116-001, 116-010, 104-040, 121-004), the significance which is uncertain to this reviewer.

Two (2) subjects (116-001, 116-007) developed "*abnormal thinking*", one (116-007) with *decreased concentration*,16 lb weight loss and weakness (asthenia); and one (116-001) with headache and *hypertonia* (clenching of fists and jaw). Two additional subjects developed *hypertonia* (106-009, 129-031) both associated with headaches. Subject 106-009 had flat T waves at baseline, but, no follow-up ECG is included contextually in the vignette to determine full, clinical significance.

Several *new medico-psychiatric symptoms* were reported in seven (7) of these subjects who left Study 304 because of adverse events. They were presumably screened at baseline in Study 303 by a psychiatric interview and SCID-I with HAM-A and HAM-D, for the presence to exclude co-morbid disorders which would impact on the diagnosis of ADHD. Two subjects developed *mania*. One subject(102-021) was hospitalized because of the development of hypothyroidism, suicidal ideation, poor concentration and memory difficulties, and found to be *bipolar with psychotic symptoms.* The other subject developed a *manic reaction* in the context of a *severe headache*. Five (5) subjects developed *depression* (104-040, 128-006, 128-003, 129-012, 130-014), of which, three (3) were associated with cardiovascular symptoms [prolonging of QT

(104-040), dizziness (129-012) and palpitations (130-014)] and two (2) with appetite changes [weight loss (128-003) and anorexia (129-012)].

Several adverse events were of concern and suggest differing neurological events, the mechanisms of which are uncertain from the available information (e.g. ischemia, seizure, etc). They are the development of: 1) *left upper extremity weakness with severe headaches* resulting in hospitalization(102-021); 2) a *reduction in visual acuity (mild amblyopia)* and *dizziness* (113-003); 3) *poorly visualized fundus* at baseline (uncertain, if this was a new event from Study 303) with palpitations (113-010); and 4) *bilateral numbness in hands* (hypesthesia)with *dyspnea and pain radiating to the left arm* (102-012). Another subject (126-006) had baseline *half tremor*, *somnolence, dizziness and dyspnea*. No follow-up information from the normal baseline VS and ECG's were provided to determine the clinical significance. It is unclear to this reviewer what the Sponsor means by half-tremor, or, if the subject developed the half-tremors in Study 303, or, whether it was pre-existing.

One subject (113-005) with baseline, elevated CK Levels and fibromyalgia developed worsening of the already elevated CK, headache, vasodilitation and on-going HTN (140/100). It is again, unclear to this reviewer, why this subject was allowed into the study, presumably, a protocol and GCP violation.

The nature of these individual adverse events raises concerns about both short and long-term safety of Adderall XR in the adult population. However, much information is lacking in the Sponsor provided vignette's, preventing determination of its true clinical significance.

Adverse events reported by greater than or equal to 2 % of subjects in Study 303 and 304 are indicated in Sponsor's Table 8 and 9, respectively, which are included in the Appendix. Adverse event rates are for all Adderall XR doses are combined.

In study 303, the overall event rate was 84.4 % and 56.3 % in the drug and placebo group, respectively. The most frequently occurring events in Study 303 were dry mouth (drug: 35.1%; placebo: 4.7 %), anorexia (drug: 33%; placebo: 3.1 %), insomnia (drug: 27.2 %; placebo: 12.5 %), headache (drug: 26.2%; placebo: 12.5 %), nervousness (drug: 12.6%; placebo: 12.5 %), and weight loss (drug: 10.5%; placebo: 0 %). Other events occurring more frequently in subjects on drug in Study 303 were: anxiety (drug:

7.9%; placebo: 4.7 %), agitation (drug: 7.9%; placebo: 4.7 %), dizziness (drug: 7.3%; placebo: 0 %), palpitations (drug: 4.2%; placebo: 0 %), tachycardia (drug: 6.3%; placebo: 3.1%), diarrhea (drug: 6.3%; placebo: 0 %) and nausea (drug: 8.4%; placebo: 3.1%). In Study 304, as of the 01/31/2003 cut-off date, 1022 AE's were reported for 207 (92.8%) subjects[57]. The most frequently occurring events in Study 304 were dry mouth (42.2%), anorexia (30%), insomnia (26.5%), headache (22.4%), nervousness (20.6%), and weight loss (10.3%). Less frequent AE's included anxiety (9.4%), agitation (9%), dizziness (9.4 %), nausea (9.4%), asthenia (8.1 %), depression (6.7 %) and constipation (6.3 %).

In study 304, increased duration of Adderall XR exposure resulted in the largest increases in the following reported AE's: nervousness (12.6 % to 20.6%), depression (3.1% to 6.7%), infections (4.2 % to 10.8 %), and constipation (3.7% to 6.3%).

In Study 108, the dose proportionality PK study, 12 subjects reported 156 AE's. Prominent AE's were anorexia (75.0%), asthenia (66.7%), headache (58.3%), insomnia (58.3%), dry mouth (41.7%), nausea (41.7%) paresthesia (41.7%), somnolence (41.7%), palpitation (33.3%), nervousness (33.3%), and tachycardia (25.0%).

Drug-Demographic and Drug-Disease Interactions

In order to address drug-demographic interactions, the Sponsor performed sub analyses of AEs based on gender, race and age.

- Gender: Overall, 149 men and 99 women received Adderall XR in Studies 303 and 304. Approximately, 93% of men and 97% of women reported at least one adverse event. AE's with a >5% difference between men and women with women showing a higher incidence rate were headache (29.5% for men vs. 37.4% for women), palpitation (2.7% vs. 9.1%), and anorexia (35.6% vs. 45.5%); and with men showing a higher incidence rate were nervousness (25.5% vs. 18.2%).

- Race: Overall, 221 subjects were Caucasian and 27 subjects were other races. Caucasians were more likely to report adverse events than non-Caucasians (96% vs. 89%). AE's with a >5% difference between the two race groups with Caucasians

57 Adverse events continuing from Study 303 were considered by the Sponsor as baseline medical history. Only new treatment emergent events were recorded as adverse events.

showing a higher incidence rate were constipation (Caucasians: 17.7%; others: 11.1%) and weight loss (Caucasians: 15.7%; others: 7.4%); and with all other races showing a higher incidence rate were headache (31.2% vs. 44.4%), tachycardia (5.0% vs. 14.8%), anorexia (38.5% vs. 48.1%), and nausea (12.7% vs. 22.2%). Hence, non-Caucasian may be more likely to experience anorexia, nausea, and tachycardia and less likely to experience constipation and weight loss than Caucasians. The Sponsor states that since there were only 27 non-caucasians, one must be careful in making such a conclusion.

- Age: In examining the relation between AE's and age, the Sponsor divided subjects into two (2) age groupings: 18-39 years (n=132) and ≥ 40 years (n=116). Approximately, 93% of 18 to 39-year old group and 97% of 40-year old or older group reported at least one AE. The difference in incidence rate between the two age groups receiving Adderall XR was consistent to that of placebo (18-39 yrs, 52%; vs. ≥ 40 years, 61%) which indicated to the Sponsor that "old patients were more likely to report adverse events than young patients".

  Those adverse events with a >5% difference between them was anorexia [18-39 yrs, 43.2% (drug), 0 % (placebo); vs. ≥ 40 years, 35.3% (drug), 6.5 % (placebo)], weight loss [18-39 yrs, 20.0% (drug), 0 % (placebo) vs. ≥ 40 years, 6.9% (drug), 0 % (placebo)], agitation [18-39 yrs, 8.3% (drug), 3.0 % (placebo) vs. ≥ 40 years, 14.7% (drug), 6.5% (placebo)], and insomnia [18-39 yrs, 34.1% (drug) , 6.1% (placebo) vs. ≥ 40 years, 40.5% (drug), 19.4% (placebo)]. The Sponsor concluded that young adult subjects may be more likely to experience anorexia and weight loss than older subjects.

Vital Signs: A summary of changes in vital signs (BP, pulse and weight) in Study 303 and 304 are shown in the Tables in the Appendix. The mean baseline value, endpoint value and change from baseline are shown. The Sponsor has combined the data from the Adderall XR groups.

In Study 303, there were statistically significant differences between placebo and Adderall XR groups with regard to systolic pressure [drug: 1.9 (± 12.19) mmHg; placebo: -1.9 (± 10.12) mmHg], pulse rate [drug: 5.2 (± 10.65) bpm; placebo: 1.9 (± 10.42) bpm] and weight [drug: -4.5 (± 5.00) lb; placebo: 0.2 (± 5.93) lb]. The Sponsor states that these effects were not clinically meaningful.

Review of Sponsor's Out-of-Normal-Range Vital Signs Listing (Listing 12.2) showed that out of normal vital signs occurred in 94 subjects (drug: 71; placebo: 23). Diastolic hypertension (BP > 90; 91-118) occurred in 41 subjects on drug and 12 on placebo. Systolic hypertension (BP > 160, 162-172) occurred in 4 subjects on drug and in none on placebo. Tachycardia (HR > 100 bpm, 101-137) occurred in 28 subjects on drug and in 5 on placebo. Tachypnea (RR > 20 bpm, 21-28) occurred in 23 subjects on drug and in 6 on placebo. This is depicted in the table below put together from data from Sponsor's Listing 12.2 provided in the Safety Update[58].

Table: Out-of-Normal-Range Vital Signs

Diastolic HTN		**Systolic HTN**		**Tachycardia**		**Bradycardia**		**Tachypnea**	
Drug (n=188)	Placebo (n=60)	Drug	Placebo	Drug	Placebo	Drug	Placebo	Drug	Placebo
41 (22 %)	12 (20 %)	4 (2 %)	0	28 (15 %)	5 (8.3 %)	0	1	23 (12 %)	6 (10 %)

Comment(1): An electronic dataset of the vital signs was requested from the Sponsor in order to look at changes in vital signs by dose group by week of treatment. This was received late in the review cycle. A preliminary review of this data follows.

Weekly Blood Pressures: No mean increases in SBP occurred in the placebo group. Mean SBP increased by week 3 in the 20 mg group [0.96 (p=0.049)] and returned to normal at the subsequent visit. In the 40 mg group, the SBP increased by week 3 [2.3 (p=0.086)] and worsened by week 4 [5.9 (p=0.000)]. In the 60 mg group, the SBP increased as early as week 1[1.7 (p=0.052)], and persisted at week 2 [2.2 (p=0.055)], week 3 [2.1 (p=0.058)], and week 4 [2.1 (p=0.030)].

No mean increases in DBP occurred in the placebo and 20 mg groups. In the 40 mg group, the DBP increased by week 3 [2.3 (p=0.054)] and returned to normal at the subsequent visit. In the 60 mg group [1.77 (p=0.052)], the DBP increased by week 3 and returned to normal at the subsequent visit.

Conclusion: The 40 mg group showed the largest increases in SBP at week 4 [5.9 (p=0.000)] and DBP at week 3 [2.3 (p=0.054)]. The 60 mg group showed early increases in SBP (1.7) which remained sustained with slight worsening at subsequent visits (2.1-2.2).

[58] Safety Update, Listing 12.2, Out of Normal Range Vital Signs: pgs. 5798-5805.

DBP increases occurred in the 60 mg group at week 3 (1.77) but returning to normal by study end.

Weekly Pulses: No mean increases in HR (pulse) occurred in the placebo group or the 20 mg group. Mean pulse increased as early as week 1[6.1 (p=0.052)], and persisted at week 2 [4.98 (p=0.041)], week 3 [8.8 (p=0.002], and week 4 [6.1 (p=0.002)] in the 40 mg group. The 60 mg group showed early increases in pulse [6.59 (p=0.025)] at week 1, which lessened by week 2 [3.1 (p=0.307), and increased again at week 3 [6.8 (p=0.016) and week 4 [6.79 (p=0.001)].

Conclusion: No mean increases in pulse occurred in the placebo and 20 mg groups. The 40 and 60 mg groups showed increases in pulse as early as week 1 which largely persisted till week 4. The 40 mg group showed the largest increases in pulse at week 3 [8.8 (p=0.002)].

Comment(2): "The Sponsor states that these changes in vital signs were consistent with the effects associated with amphetamine or other stimulants, and were not considered clinically meaningful[59]." It is unclear to this reviewer why this would not be clinically meaningful in the adult population studied, 18-76 years. There is ample epidemiologic literature which shows an increased risk of cardiovascular events (15 %) and stroke (67 %) based on a 4 to 5 mmHg increase in blood pressure over time[60]. These may or may not be related to the spontaneous postmaketing reports of cardiovascular adverse effects (including sudden death) and stroke reported during Adderall therapy. However, it needs to be clarified.

Electrocardiograms (ECG's): Summaries of mean changes of ECG parameters[61] for Study 303 and 304 are included in the Appendix. Study 303 showed statistical differences between placebo and drug with regard to changes in QT interval (-8.3 msec for Adderall XR vs. 2.9 msec for placebo) and QTc interval (4.5 msec for Adderall XR vs. -2.8 msec for placebo). For the drug group, the maximum value obtained at endpoint was 436 msec for QT interval (vs. a baseline maximum of 461 msec) and 476 msec for QTc interval (vs. a baseline maximum of 453 msec). For placebo

59 4 Month Safety Update-Adult sNDA, pg. 54.

60 Collins R, Peto R, MacMohan S, et al. Epidemiology. Blood pressure, stroke and coronary heart disease. Part 2, short-term reductions in blood pressure: an overview of randomized drug trials in their epidemiological context. Lancet 1990; 335:827-38

61 ECG Parameters: PR interval, QRS duration, QT interval and QTc interval

group, the maximum value obtained at endpoint was 433 msec for QT interval (vs. a baseline maximum of 438 msec) and 430 msec for QTc interval (vs. a baseline maximum of 440 msec). The Sponsor stated that these were not clinically meaningful changes.

In the long-term study (304), the only change in ECG parameters from the original sNDA to the current update was a mean increase of 5.6-msec from baseline in QTc interval seen in the current update, compared to a 2.5-msec increase seen in the original sNDA. The maximum value obtained at endpoint was 467 msec for QT interval (vs. a baseline maximum of 436 msec) and 472 msec for QTc interval (vs. a baseline maximum of 476 msec).

Review of sponsor's ECG Data Listing (Listing 14.1) showed that subjects on Adderall XR had more gross ECG abnormalities than subjects on placebo (drug: 53, placebo: 9). Normal baseline ECG's became abnormal in 34 subjects on drugs compared to 3 on placebo. Conversely, abnormal baseline ECG's normalized in 10 subjects on drug and 2 on placebo. In 9 subjects, on drug (compared to 4 on placebo), baseline abnormal ECG's remained abnormal (drug: 7, placebo: 4) or showed increased abnormalities (drug: 2, placebo: 0). This is show in the table below put together from data from Sponsor's Listing 14.1 provided in the Safety Update[62].

Table: ECG Data: Adderall XR (N=166) and Placebo (N=57)

ECG Δ Nl to Abn		**ECG Δ Abn to Nl**		**ECG Δ Abn to Abn**		**ECG Δ Abn to Increased Abn**	
Drug	Placebo	Drug	Placebo	Drug	Placebo	Drug	Placebo
34	3	10	2	7	4	2	0

Subjects on drug showed more T and ST wave abnormalities [flattening of the T waves (8), non-specific T waves (5), non-specific ST wave depression (3)] than subjects on placebo [non-specific T waves (1)]; more sinus tachycardia (drugs: 9, placebo: 1) compared to placebo; more rhythm abnormalities [arrhythmia VPC's (drugs: 5, placebo: 0) and APC's (drugs: 2, placebo: 0) ; and more conduction defects [branch blocks (5), others (2)] than placebo [branch block (1)]. Subjects on drug and on placebo had roughly an equal representation of the following abnormalities: hypertrophy (LAH, LVH), sinus bradycardia and sinus arrhythmias. This is show in the table below put together from data from Sponsor's Listing 14.1.

62 Safety Update, Listing 14.1, Electrocardiogram (ECG) Data: pgs. 5918-5966.

	Drug	Placebo
Changes in Waves		
Flat T Waves	8	
Non-specific T wave	2 Normal (2)	1
Non specific ST wave depression	1 Normal (1)	
Non specific ST to marked sinus arrhythmia	1	
Non specific T wave	1	
Long QT		
Short PR	2	1
Sinus arrhythmia, low voltage QRS	Normal (1)	
LAH	1	1
LVH	1	1
Rhythm Abnormalities		
Sinus tachycardia	9	1
Sinus bradycardia	8	7
Sinus bradycardia with sinus arrhythmia	2	
Sinus rhythm with arrhythmia	1	
Sinus arrhythmia	0	2
Sinus bradycardia w early repolarization	Normal (1)	
Early repolarization	1	1
Arrhythmia	5	
VPC		
PVC's to normal	1	
APC	2	
Ectopic atrial rhythm	1	1
Conduction Defects		
Incomplete RBBB	1	
I RBBB, flat T waves	1	
To sinus arrhythmia		
First Degree Block	No Δ (1)	1

	Normal (1) 1	
RV conduction delay	1	
Supraventricular extra systoles with conduction defect	1	
LAH Conduction	0	1

Comment: Review of the original NDA review for Adderall XR[63] indicates that "there were treatment emergent ECG abnormalities of various types reported in 37 drug treated patients; however, the sponsor stated that all ECG abnormalities were considered clinically insignificant although some were referred to a cardiologist for a second reading."

In Study 303 and 304, ECG abnormalities again are more prominent in subjects on drug than placebo and may be more of a concern in the context of post-marketing AE's.

Laboratory Changes in Phase III Controlled Trials

Clinical Chemistry: In Study 303, the results of clinical chemistry tests with statistically significant changes from baseline to endpoint consisted of reductions in mean serum cholesterol, VLDL and triglyceride levels. Mean cholesterol levels were just above 200 mgldL at baseline in each treatment group and decreased 7% to 9% in each of the drug groups. Triglycerides decreased 16.5%, 14.1%, and 23.4% in the 20, 40, and 60 mg groups, respectively. Although statistically significant, mean changes were marginal and not clinically significant. Please refer to the Table in the Appendix.

Each of the Adderall XR groups had subjects with new abnormalities in total bilirubin (1.2 %, 8.2 % and 3.4 %) but these changes were unaccompanied by changes in liver enzymes.

In Study 303, one subject (122-008) was discontinued from the study because of increasing liver enzymes. A vignette for that subject is included in Section XI, B [Subjects Who Discontinued Because of An Adverse Event (Study 303)]. Another subject (112-023) in Study 304 was discontinued from the study because of elevation of liver enzymes. A vignette for that subject is included in Section XI, C [Subjects Who Discontinued Because of An Adverse Event (Study 304)].

63 Mosholder AD. NDA 303: Review and Evaluation of Clinical Data.; Section 8.5.4, Electrocardiograms, pg. 16; 07/24/2001.

In Study 304, 19.4 % of the subjects had new increases in cholesterol, and 7.9 % had new increases in SGPT from baseline.

Hematology: The only hematology parameter for which there were statistically significant differences in mean values was eosinophil count. Although the decreases were statistically significant for the 40 (-0.3± 1.38) and 60 mg (-0.6 ± 1.36) groups, the changes were marginal and not clinically significant.

Urinalysis: Urinary ketones and leukocytes were present slightly more often in the Adderall XR than the placebo groups (ketones: 8.8 % vs. 3.1 %; leukocytes: 7.4 % vs. 3.2%). No other remarkable differences were present between drug and placebo groups.

Comparison of Adverse Events in Adults with Children: The Sponsor states that "the most frequently reported adverse events in all adult patients exposed to ADDERALL XR® were characteristic of amphetamine and largely consistent with the current labeling for ADDERALL XR® and ADDERALL® in treatment of children with ADHD, with the exception of dry mouth and headache. The incidence rates for the most frequent adverse events were as the following:

COSTART AE's	303 (n=191)	304 (n=223) (original sNDA)	304 (n=223) (current update)
Dry mouth	35.1%	42.2%	42.2%
Anorexia	33.0%	29.6%	30.0%
Insomnia	27.2%	25.1%	26.5%
Headache	26.2%	21.1%	22.4%
Nervousness	12.6%	18.4%	20.6%
Weight loss	10.5%	9.0%	10.3%
Infection	4.2%	9.9%	10.8%

Comparison of the adverse events on the labeling between children and adults showed the following adverse events to have occurred much more frequently in adults than in children: headaches (adults: drug: 26 %, placebo: 13 %; children: 0%), dry mouth (adults: drug: 35%, placebo: 5%; children: 0%), anorexia\loss of appetite (adults: drug: 33%, placebo:3%; children: 22%, placebo: 2 %), diarrhea (adults: drug: 6%, placebo:0%; children: 2%, placebo: 1%), dizziness (adults: drug: 7%, placebo:0%; children: 2%, placebo: 0 %), tachycardia

(adults: drug: 6%, placebo:3%; children: 0%), agitation (adults: drug: 8%, placebo:5%; children: 0%), weight loss (adults: drug: 11%, placebo:0%; children: 4%, placebo: 0 %), and urinary tract infections (adults: drug: 5%, placebo:0%; children: 0 %).

Adverse Events in Labeling:

The Sponsor wants to include the following adverse event information from Study 303 in the labeling. This information reflects adverse events reported by 5% or more adults receiving Adderall XR with a higher incidence than placebo. The Sponsor states that "although the safety information is available to evaluate the long-term use of ADDERALL XR® in patients, comparisons of safety data between ADDERALL XR® vs. placebo should be limited to SLI 381.303 only in the Phase 3 pool as it was performed in the original sNDA. Other comparisons are not appropriate since safety data on the long-term use of placebo were not collected and the safety data reported in this update did not take the length of patients' drug exposure into consideration."

Body System	Preferred Term	ADDERALL XR™ (n=191)	Placebo (n=64)
General	Asthenia	6%	5%
	Headache	26%	13%
Digestive System	Loss of Appetite	33%	3%
	Diarrhea	6%	0%
	Dry Mouth	35%	5%
	Nausea	8%	3%
Nervous System	Agitation	8%	5%
	Anxiety	8%	5%
	Dizziness	7%	0%
	Insomnia	27%	13%
Cardiovascular System	Tachycardia	6%	3%
Metabolic/Nutritional	Weight Loss	11%	0%
Urogenital System	Urinary Tract Infection	5%	0%

Comment: There are no large differences except that nervousness (20.6%), or, that increased anxiety and depression with longer use of treatment would not be appropriately represented in labeling. Anxiety and nervousness need to be re-coded in the 303 and considered as one term. The open-label, pre-marketing, other adverse events should adequately be made to reflect these concerns. Currently, it is not.

D. Adequacy of Safety Testing

Blood pressure was not an endpoint, hence, these trials were not designed to look at changes in blood pressure (e.g. average of 3 samples).

No dynamic studies were done to evaluate cardiovascular function of subjects on Adderall XR , especially given the post-marketing observation that exercise may increase the risk of an adverse event. These may need to include a cardiac stress test, holter and vital sign monitoring.

Further evaluation is needed of the ECG's given the treatment emergent changes observed in the adult and pediatric trials.

The duration of exposure for all subjects at all doses is inadequate.

E. Post-Marketing AERS

Sympathomimetic(s) have been associated with focal arterial vasoconstriction and vasculitis in different parts of the vascular tree. Myocardial infractions, strokes, seizures, ischemic bowel disease, etc., have been associated with therapeutic and, or, non-therapeutic use of stimulants. Recently, ephedra has been implicated in myocardial infarctions, cerebrovascular accidents and seizures in persons aged 30 years of younger (50 % of the cases). Some of these events were associated with physical exertion. In order to determine the safety of Adderall XR for Adult ADHD use, select cases in AERS were identified and reviewed, in order to identify potential risks which may be associated with longer use than the 4 week efficacy trial (303) and open label follow-up extension (304). The identified events consisted of seizures, deaths (pediatric-adolescent), deaths (adults), strokes, myocardial infarctions; arrhythmias in adults, not resulting in death; probably arrhythmias in all patients, not resulting in death; arrhythmias in all patients, resulting in death and not resulting in death; cardiomyopathy; ischemic bowel disease; and vasomotor instability. Each of these events is summarized in the following sections with a summary following each type of adverse event.

Twenty-four (24) deaths were identified in patients who had taken Adderall, fifteen (15) with pediatric-adolescent use, and nine (9) with adult use. Mean age at the time of death was 12.6 and 37.3 years in the pediatric–adolescent and adult patients, respectively. Of the pediatric-adolescent deaths, 12/15 were sudden, occurring with therapeutic doses (10/15) at prolonged treatment (40.5 mths in 8/15) and in the context of physical exertion (6/15). An arrhythmia was thought or determined to be the cause of death in 6/15. Concurrent medication use was present in 4/15 patients and was unknown in 5/15 patients. In 6/15 patients there was no other medications. All pediatric-adolescent deaths occurred in males. Of the adult deaths, 4/9 were sudden, occurring with therapeutic dose (4/9); with both short [4/9(3.87 mths)] and long duration of treatment [2/9(36 mths)]; in the context of physical exertion (2/9). No identifiable risk factors were present in 5/9 patients.

Concurrent medications use, occurred in 6/9 patients. Sex distribution was 5 male and 4 females. Strokes, ischemic bowel disease and vasomotor instability seemed to occur much more frequently in females compared to males.

Table: Summary of Post-Marketing AERS

Event	#	Mean Age	Sex	Dose	Duration (Avg)	Risk Factors	Other Meds	Type
Seizures	7	24.8	4 M 3 F	Nl (5) ? (2)	36 mths (2) 4.5 mths (5) ? (1)	None 2 Head Injury: 1 Migraines: 1 Mentally Disabled: 1 ?: 2	Yes (1) No (3) ? (3)	Partial: (3) Generalized: (1) ?: 3
Deaths Pediatric/ Adolescent	15	12.6	15 M 0 F	Nl (10) ? (5)	40.5 mths (8) < 6 mths (3) ? (4)	Physical Exertion (6) Sleep (3) Unknown heart disease (1) Heat Exposure/Dehydration (1) Yes (2)	Yes (4) No (6) ? (5)	Sudden (12) *Arrhythmia (6)* *Hypertrophy (2)* *Heart Disease (1)* Suicides (3)
Deaths Adults	9	37.33	5 M 4 F	Nl: 4 ?: 5	36 mths: (2) 3.87 mths (4) ?: (3)	Physical Exertion (N=2) None: (5) Cardiomyopathy/Arrhythmia (1) Sleep apnea/HTN (1)	Yes (6) No (1) ? (2)	Sudden (4) *Arrhythmia (1)* *Hypertrophy (1)* *Heart Disease (1)* Stroke (2) Suicide (1)
Strokes	8	37.4	2 M 6 F	Nl (7) ? (1)	37.92 mths (3) < 1 yr (3) ? (2)	None (5) Cardiomyopathy/Arrhythmia (1) HTN (1)	Yes (2) No (4) ? (2)	Lacunes (2) Subarachnoid (1)
MI's	6	42.6	5 M 1 F	Nl (3) ? (3)	36 mths (1) < 0.5 mth (2) ? (3)	Physical Exertion (2) Yes (3)	Yes (2) No (2) ? (2)	Vessels Nl (1)
Arrhythmias Adults (Non-Death)	6	42.25	6 M 2 F	Nl (3) ? (3)	36 mths: 2 ?: 4	None: 3 Previous Cardiac: 3 Physical Exertion: 1	Yes (1) No (1) ? (4)	Vessels Nl (1) Inflammation around heart" (1) Arrest (2) SVT's (2) PVC's (1)
Arrhythmias/All Non-Death,	13	25.72	12 M	Nl: 8 ?: 5	38.4 mths: 5 9 mths: 1	None: 2 Physical Exertion: 5	Yes (2) No (5)	Sudden Death (7) Resuscitation (2)

Death (Probable)			1 F		1 dose: 1 ?: 6	Previous Cardiac: 3 Sleep Apnea: 1 Heart Murmurs: 2 Occult Heart: 1	? (6)	Cardioversion (1) Vessels Nl (1) Hypertrophy (2) IHSS (1) Abn. Valve (1) SVT (2) VFib (1)
Arrhythmias/All Non-Death, Death (Probable + Possible)	21	21.78	17 M 4 F	Nl: 11 ?: 10	42 mths: 9 6.3 mths: 3 1 dose: 1 ?: 8	None: 4 Physical Exertion: 7 Previous Cardiac: 3 Sleep Apnea: 1 Heart Murmurs: 2 Occult Heart: 1	Yes: 7 No: 7 ?: 7	Sudden Death (14) Resuscitation (2) Cardioversion (1) Vessels Nl (1) Hypertrophy (2) Cardiomyopathy (1) IHSS (1) Abn. Valve (1) SVT (2) VFib (1)
Cardiomyopathy	5	28.75	3 M 2 F	High (1) Nl (3) ? (1)	2.25 yrs (2) 2 mth (1) ? (1)	Adriamycin cardiomyopathy w/ Arrhythmia (1) No (1) ? (3)	Yes (3-4) ? (1)	Heart Transplant (2 ?) Stroke (1) Death (2) ?: 1
Ischemic Bowel Disease	1	19	1 F	Nl (1)	3 yrs (1)	Yes (1)	Yes (1)	Gut (1) Colostomy Worse DM Control
Vasomotor Instability	7	33.5	1 M 6 F	Nl (4) ? (3)	< 4 mth (3) ? (4)	Cigarettes (1) Hypothyroid (1) ? (5)	No (1) Yes (2) ? (4)	Cyanotic Extremities (3) Thrombosis toes (1)

1. Seizures (New Onset)

CSENUM 3193029, MFR No: 97100601: 25 year old female with ADD on Adderall 40 mg QD X 2 months developed a new onset seizure (scream followed by loss of consciousness). Past medical history was unremarkable. Neither the patient nor other family members had a history of seizures. She was on no other medications. The patient recovered. Same as Case No. 3153943.

CSENUM 3193058, MFR No: 97102301: 36 year old male with ADHD on Adderall 10 mg BID X 2 weeks and had a major motor seizure. The patient had no past history of seizures but did have a severe head injury 10 years prior with apparent neurological sequel. He was on no other medications. The patient recovered. Same as Case No: 3153949.

CSENUM 3442762, MFR No: US00028: 20 year old male with ADHD on Adderall 10-20 mg QD X 6 months with new onset seizure (aura, loss of consciousness, tonic component). Blood work and CCT scan performed in the emergency room were reported to be normal. The patient had no history of seizures, no significant medical history and was on no other medications. The patient recovered. Same as Case No. 3471044.

CSENUM 3817876 MFR No: US00214500:21 year old female on Adderall X 1 year (dose and indication are uncertain) with a new onset seizure. A workup consisting of an EEG and an MRI were reported to be normal. Neither the patient nor other family members had a history of seizures. Her past medical history and her family history were remarkable for migraines. Other medications that the patient takes (? PRN) were hydrocodone, ibuprofen and Imitrex (sumatriptan succinate). Same as Case No. 3947925.

Report No: 4018067 MFR No: US0221900: 24 year old female, mentally disabled on Adderall 15 mg BID X 4 years had a new onset seizure while sleeping. The patient was started on Tegretol and a work-up (MRI) was started. No other information was provided.

Report No: 3933486 MFR No: US0213600: Male patient (age uncertain, ? adult) took Adderall (dose, duration uncertain) for uncertain reasons and had a seizure. An EEG was obtained which was abnormal, consistent with a "seizure disorder."

Report No: 4154721 MFR No: SUSI-2003-00040: 23 year old female on Adderall 10 mg BID X 2 years for ADHD, developed nocturnal seizures (diagnosed as temporal lobe), 1-2 months after starting Adderall. Patient was placed on clonazepam and subsequently switched to oxcarbazepine without a clear change on seizure frequency. Diagnostic studies, consisting of an MRI and an EEG were reportedly normal.

CSENUM 3841882 MFR No: US0229400: 7.5 year old male with ADHD on Adderall XR X 3 days (switched from Concerta) with possible short seizure (eyes open, staring straight ahead and non-responsive). Patient had bronchial asthma but had not received any medications (type not specified) at the time of the event.

CSENUM 3969194 MFR No: SUS1-2003-00120: 11 year old male with ADHD, previously treated with a long acting methylphenidate, was placed on Adderall XR 10-30 mg X 3 months when he had a new onset seizure. Laboratory tests were normal and no previous medical history was identified.

- **Seizures (New Onset, Overdose)**

CSENUM 3475955 MFR No: US0007700: 18 year old female took 33 0f her brother's Adderall 10 mg tablets in an unsuccessful suicide attempt and had several seizures. In the ER, the patient was given activated charcoal and intubated. She recovered. No further information was provided. Same as Case No. 3502765.

CSENUM 3702009 MFR No: US0120200: 35 year old male apparently took an overdose (dose and amount uncertain) of Adderall, Meridia (sibutramine) and Claritin (loratadine) and developed tonic clonic seizures which were followed by agitation, hypertension (200/100) and tachycardia. Following the event he complained of depression and a mild headache. Same as Case No. 3783319.

- **Seizures (Known)**

CSENUM 3193125, MFR No: 97121201: 25 year old male with ADHD on Adderall 10 mg TID X 1 year and Tegretol (carbamazepine) X 13 years for a know seizure disorder, had a breakthrough seizure. He was found to be sub-therapeutic on his Tegretol. Same as Case No. 3153973.

- **Seizures (Possible)**

Report No: 3522716 MFR No: US9911500: 40 year old female on Adderall 10 mg (duration uncertain) for ADHD was reported to be in a stupor. No other information was provided except that the weight indicated that the patient was obese (285 lbs).

CSENUM 3742781 MFR No: US0101200: 6 year old male with ADHD, ODD on Adderall XR 10 mg X 2 days with possible seizure ("jerky movements and eye rolling"). Patient had tics and eye rolling behaviors prior to starting Adderall XR. Work-up consisting of EEG and CCT scan were normal.

Report No: 3153943 MFR No: 97100601: 25 year old female on Adderall 20 mg (duration uncertain) was reported to have convulsions and have been in a coma. No further information was provided.

Report No: 3522644 MFR No: US0001600: Patient (age and sex, not specified) on Adderall 10 mg (duration uncertain) was reported to have a seizure. No other information was provided.

Report No: 3153973 MFR No: 97121201: 25 year old male on Adderall 10 mg (duration uncertain) and Tegretol (dose and duration uncertain) was reported to have a convulsion. No other information was provided.

Report No: 3154554 MFR No: 97121202: Male patient (age uncertain) on Adderall (dose and duration uncertain) and Depakote (dose and duration uncertain) was reported to have a convulsion. No other information was provided.

Report No: 3479034 MFR No: 00031501: Child (sex and age uncertain) on Adderall 20 mg/day for ADHD X 3 weeks (duration uncertain) and dose was increased to 40 mg/day, following which the child had a seizure. No other information was provided.

Summary of New Onset Seizures in Adult AERS

Seven (7) patients (4 M, 3 F; avg: 24.8 yrs) with new onset seizure were identified in adult patients taking therapeutic doses of Adderall for ADHD. By history, three of the patients had partial seizures with

secondary generalization consistent with a focal origin; one had a generalized seizure; and insufficient information was present on the other 3 patients. Two patients had no identifiable risk or other predisposing factors, two had relative associated risk factors (mentally disabled, migraines), one had a definite risk factor (significant prior head injury), and no information was present on the other 2 patients. On the average, the duration of treatment prior to seizure onset was 4.5 mths in 5 patients, 36 mths in 2 patients, and unknown in the other. Two (2), additional adult patients developed new onset seizures when they took an overdose of Adderall, alone, or, in combination with other drugs. One (1) additional adult patient with a know seizure disorder had a breakthrough seizure secondary to sub-therapeutic Tegretol.

Table: Summary of Seizures (New Onset) in Adults: Post-Marketing AERS

Age	Sex	Dose	Duration	Risk Factors	Other Meds	Type	Outcome
25	F	40 mg QD	2 mths	None	None	Partial w/ SG	
36	M	10 mg BID	2 weeks	Prior head injury	None	Generalized, motor	
20	M	10-20 mg QD	6 mths	None	None	Partial w/ SG	CCT (-)
21	F	?	1 yr	Migraines	Yes (PRN)	?	EEG (-), MRI (-)
24	F	15 mg BID	4 yrs	Mentally disabled	?	?	
?	M	?	?	?	?	?	EEG (+)
23	F	10 mg BID	2 yrs 1-2 mth onset	?	?	TLE	EEG (-), MRI (-)
24.8 yrs (Avg)	**F: 4 M: 3**	**Nl (5) ? (2)**	**36 mths (2) 4.5 mths (5) ? (1)**	**Head Injury: 1 Migraines: 1 Mentally Disabled: 1 None: 2 ? :2**	**Yes (1) No (3) ? (3)**	**Partial: (3) Generalized: (1) ?: 3**	**MRI/CCT: Neg (3) EEG: Neg (2) EEG: Pos (1)**

2. Deaths

- **Children and Adolescents**

CSENUM 3789498, MFR No: 01P-163-0110393-00: 14 year old male on 30 mg Obetrol (duration uncertain) and VPA X 6-7 mths for PTSD was given 50 mg Obetrol on day of event. In a boot camp, the child was being disciplined in hot surroundings, developed hyperthermia, became tachycardic (HR 161) and delirious. While being cooled off in a bath, the child apparently drowned. Developed seizures at the hospital and died within 24 hours. No past medical history was available, except a weight of 205 lbs (no height is noted). Autopsy showed that the cause of death was near drowning and dehydration due to heat exposure. Same as 3788756, US0121100.

CSENUM 3838254: 12 year old male on Adderall 30 mg QD X 18 mths for ADD. Patient developed worsening depression on medication and committed suicide by hanging self in oppositional rage.

CSENUM 4049232, MFR No: US0301000: 13 year old male on Adderall for ADHD (dose and duration, uncertain) had an argument with mother and hanged self.

CSENUM 4070563, MFR No: US0306800: 16 year old male on Adderall XR 30 mg X 3 mths, 6-7 mths drug holiday, restarted X 1 week, then committed suicide with his father's gun. Concurrent medications included clonidine (dose, duration and reasons, unknown). No **past** medical history is present. This case is apparently under litigation with the plaintiff claiming that "the teenager suffered from major depression exacerbated by Adderall."

CSENUM 3731168, MFR No: US0112700: 16 year old male on Adderall 10 mg (dose and duration, uncertain) and Zyprexa (dose and duration, uncertain) and the patient died suddenly. No further information was provided.

> *Case No. 1: ODS Post-Marketing Safety review of Sudden Deaths: 0/16/2002: 16 year old male who had been taking Adderall for ADD (2 years) and Zyprexa for a personality disorder (1-2 years). This patient was found dead on the floor next to his bed, and the autopsy revealed hepatic steatosis. The reporting physician indicated that there may have been an interaction between the two medications, but there was no evidence of an interaction. Further information was not available.*

CSENUM 3789506, MFR No: US0121600: 11 year old male on Adderall 10 mg BID X 4 years for ADHD. Adderall was stopped for unclear reasons, 2 days prior to death. The patient died in his sleep. Amphetamine level at autopsy was toxic (900-1000). No renal or hepatic abnormalities were noted. The child had insulin dependent diabetes.

CSENUM 3978812, MFR No: US0218000: 11 year old male on Adderall 20 mg QD for "some time" (duration, uncertain) for ADHD, collapsed during activities at Camp. The autopsy revealed an amphetamine level of 210 ng/ml, with toxic levels being ≥ 150 ng/ml. The number of pills in the child's vial was determined to be accurate, according to amount and dosing schedule, and analysis of the pills showed them to be correctly labeled, as to medication and concentration. He was taking a generic form at the time of the last refill. Autopsy showed severe pulmonary aspiration pneumonia. The pathologist concluded that "the child died as a result of cardiopulmonary arrest due to cardiac arrhythmia due to an elevation of the level of amphetamine." Same as Report No: 3982225, US0218001.

CSENUM 3811155, MFR No: US0125300:7 year old male on Adderall (dose and duration, unknown) for ADHD. Patient had a known heart murmur. The patient was found dead in his bed. Amphetamine level at autopsy was normal. He was found to have a bicuspid aortic valve. "The coroner thought that the child died from an arrhythmia."

CSENUM 3818607, MFR No: US0127000:10 year old male on Adderall (dose unknown) X 8 years collapsed and died on a soccer field. No other information was available.

CSENUM 3459227:10 year old male on Adderall (10 mg BID) X 6 mths for ADD. Patient was athletic but drowned in a shallow pond when swimming with fellow campers, when mother briefly turned away.

CSENUM 3859036, MFR No: US0120601:13 year old male with ADHD received one dose of Adderall 20 mg for ADHD, several hours later, complained of fatigue, and collapsed. He was dead upon arrival to the hospital. Pre-medical medical exam showed a normal blood pressure and heart rate. The patient was described as being active in sports. Autopsy showed low amphetamine levels and hypertrophic cardiomyopathy secondary to idiopathic hypertrophic subaortic stenosis (IHSS). It was felt that the amphetamine may have caused an arrhythmia but did not cause the enlarged heart.

CSENUM 3887728, MFR No: JS0205700[64]: 14 year old male who had been taking Adderall (dose uncertain) for approximately three years for ADD, experienced shortness of breath and collapsed during the exercises for his ROTC class. He then experienced a full cardiac arrest and was pronounced dead 1 hour later. He had a history of a heart murmur and scoliosis. Cardiac tests performed three years prior did not reveal any sign of heart disease. The autopsy report revealed an amphetamine level of 0.22 mg/L, and the pathologist commented that the "subject died as a result of a cardiac arrhythmia due to "amphetamine-related cardiac hypertrophy." The level of amphetamine in the blood at the time of death was higher than would be generally expected with a therapeutic does." He also added that the cardiac hypertrophy was "due to chronic amphetamine toxicity." The report did not provide Adderall doses used in this patient, but the duration of therapy was three years. He had been on Ritalin in the past but was switched to Adderall.

CSENUM 3555682, MFR No: US0013000: 15 year old male with ADHD who had been taking Adderall 20 mg X 3 years, collapsed while playing basketball in school. He could not be resuscitated. The cause of death was attributed to an arrhythmia caused by an increased density around the heart." Past medical history was remarkable for a heart murmur till two years of age. He was in good health, and there was no family history of cardiac disease. He was on no other medications.

CSENUM 3613516, MFR No: US0019800: 15 year old male on Adderall 20 mg QD for ADHD for 18 months suddenly died. He was found dead of unknown causes. Post-mortem autopsy showed no gross organ abnormalities, including his heart. A toxicology screen was negative. The only significant post-mortem finding, based on tissue assay, was neurtropenia. The patient had no prior history of neurtropenia. He was on no other medications.

CSENUM 3972359, MFR No: US0229000: 12 year old boy on Ritalin (dose uncertain) X 4 years for ADHD, was switched to Adderall XR 10 mg. Patient received one dose and several hours alter while running 1-2 miles, cross-country, collapsed, and could not be revived. Autopsy and drug screen results were obtained but not part of the report. The child was on no other medications and his past medical history was unremarkable. Family history was remarkable for child's mother having an arrhythmia (ventricular tachycardia) requiring implantation of a defibrillator and then surgical ablation.

64 Case No. 5: ODS Post-Marketing Safety Review of Sudden Deaths: 0/16/2002

Summary of Pediatric and Adolescent Deaths on Adderall in AERS

Fifteen (15) deaths occurred in pediatric or adolescent male patients (15 M, 0 F; avg: 12.6 yrs) taking Adderall IR or XR. Of these fifteen (15) deaths, twelve (12) were sudden, and three (3) were suicides. Six (6) of the sudden deaths died during normal, physical exercise. Three (3) died during sleep or were found dead next to their bed. Of the other three (3) children, one had unknown heart disease (IHSS) and collapsed and died after receiving a single dose; another died suddenly (no details available) and essentially had a normal autopsy (except, for tissue neurtropenia); and another died while being disciplined at a boot camp from dehydration secondary to heat exposure. Three (3) others committed suicide presumably related to worsening dysthymia or oppositional rage. Ten (10) of the patients appeared to be on therapeutic doses of drug, and no information on drug dose was available on five (5).

Duration of therapy was from 1.5-8 years (avg: 40.5 mths) in eight (8) patients, unknown in five (5), and less than 6 months in three (3) [avg: 3 mths]. Six (6) patients were on no concurrent medications, four (4) were on other drugs, and no information was provided on five (5) patients. Clearly recognized risk factors were only present in one (1) patient (unknown heart disease: Idiopathic Hypertrophic Subaortic Stenosis), and a relative risk factor in another (heart murmur). Two patients had higher than expected post-mortem blood levels of amphetamines on therapeutic doses, the significance which is uncertain. One patient had insulin dependent diabetes and another had just taken his first dose of a generic version of the drug after having been previously on 20 mg of Adderall IR for "some time." In six (6) patients, an arrhythmia related to Adderall use was thought to have resulted in the death. Cardiac findings on autopsy consisted of hypertrophy in a patient on drug for 3 years, "increased heart density" in another patient on drug for 3 years, Idiopathic Hypertrophic Subaortic Stenosis (IHSS) in a patient just taking one (1) dose, and a bicuspid aortic valve in a child who died in his sleep.

Table: Summary of Pediatric and Adolescent Deaths and Adderall Use: Post-Marketing AERS

Age	Sex	Dose	Duration	Risk Factors	Other Meds	Type	Outcome
14	M	30 mg 50 mg DOE	?	Hyperthermia Dehydration	VPA X 6.5 mth	Dehydration from hyperthermia, near drowning	Death
12	*M*	*30 mg*	*18 mths*	*Dysthymia*	*?*	*Suicide (hanging)*	*Death*
13	*M*	*?*	*?*	*?*	*?*	*Suicide (hanging)*	*Death*
16	*M*	*30 mg XR*	*3 mths, then 1 week*	*Major depressive disorder*	*Clonidine*	*Suicide (gunshot)*	*Death*
16	M	10 mg	?	?	Zyprexa		Sudden death
16	M	?	2 years	?	Zyprexa	Hepatic steatosis	Found dead next to bed
11	M	10 mg BID	4 yrs	IDDM	Insulin	Amphetamine toxicity	Sudden death in sleep ? Suicide
11	M	20 mg IR Generic (1 dose)	? "some time"	Physical Exertion	?	Collapsed during activities at camp Arrhythmia Amphetamine Toxicity with normal use	Sudden Death
7	M	?	?	Heart murmur	?	Bicuspid aortic valve Arrhythmia	Sudden death in sleep
10	M	?	8 yrs	Physical Exertion	?	Died during sports	Sudden Death
10	M	10 mg BID	6 mths	Physical Exertion	None	Athletic child who died while swimming in shallow water	Sudden Death?
13	M	20 mg	1 dose	Idiopathic Hypertrophic Subaortic Stenosis (IHSS)	None	Athletic child who collapsed and died after dosing	Sudden Death

						IHSS Arrhythmia	
14	M	?	3 years	Physical Exertion Heart murmur (RRF)	None	Arrhythmia Cardiac Hypertrophy From Chronic Amphetamine	Sudden Death
15	M	20 mg	3 years	Physical Exertion Resolved heart murmur (RRF)	None	Arrhythmia Increased " heart density"	Sudden Death
15	M	20 mg	18 mths	?	None	Autopsy normal except for tissue neurtropenia.	Sudden Death
12	M	Ritalin (dose?) 10 mg (XR)	4 yrs 1 dose	Physical Exertion Arrhythmia-Mother (RRF)	None	Collapsed while running cross country	Sudden Death
12.6 yrs (Avg)	**M: 15 F: 0**	**Nl: 10 ?: (5)**	**40.5 mths (8) < 6 mths (3) ? (4)**	**Physical Exertion (6) Sleep (3) Unknown heart disease (1) Heat Exposure/Dehydration (1) Yes (2)**	**None: 6 Meds: 4 ?: 5**		**Sudden (12) *Arrhythmia (6)* *Hypertrophy (2)* *Heart Disease (1)* Suicides (3)**

- **Adults**

CSENUM 3003088, MFR No: 112597A: 51 year old male with ADD on Adderall 20 mg TID X 3 years died from a stroke. He may have had a history of cardiovascular problems. No information on the autopsy was provided.

CSENUM 3206763, MFR No: US9908800: 62 year old male with ADD on Adderall (10 mg AM, 5 mg PM) X 13 days had a MI while shoveling snow. The patient was last seen by his physician 2 weeks prior to the event and he did not have any active co-morbid health conditions, except for mild hypertension (155/95) and a weight of 210 lbs (height not available). Past medical history was remarkable for a history of alcoholism 9 years prior and poor dietary habits (?). No information on an autopsy was provided (Same as: 3195487)

CSENUM 3528625, MFR No: US0013200: 22 year old female was on Wellbutrin (Bupropion) X 8 months, when Adderall (dose unknown) was added to her therapy X 4 months. She was found dead in a community home where she lived. No information on the autopsy was provided. Same as Case No: 3534227.

CSENUM 3625300, MFR No: US0104001: 28 year old female on Celexa (dose and duration unknown) and Adderall (dose and duration unknown) experienced flu-like symptoms, chest pain and suddenly died. No information on the autopsy was provided.

CSENUM 3919502, MFR No: US0303900: 36 year old female on Adderall XR X 2 months (5 mg to 30 mg BID) to enhance the effects of pain medications developed nausea, stomach pain and fatigue and went into a cardiac arrest X 30 minutes following resuscitation efforts. She developed an anoxic encephalopathy, placed on a ventilator, and was subsequently removed. She was found to have a *small subarachnoid hemorrhage*. Death was attributed to a combination of Adderall and Elavil with a know cardiomyopathy. Past medical history was remarkable for a history of osteosarcoma at age 15 years; Adriamycin (doxorubicin) induced cardiomyopathy; severe tachycardia, possibly the result of an accessory pathway; severe depression with 2 prior suicide attempts. Concurrent medications included: Elavil (amitripyline) 200 mg HS, Toradol (Ketorolac tromethamine) injectable 30 mg BID QOD, Toradol 10 mg QID, Effexor XR (venlafaxine) 200 mg, Ativan (lorazepam) 2 mg QID and methadone 10 mg QD. Same as Case No. 4074653.

Case No. 4: ODS Post-Marketing Safety review of Sudden Deaths: 0/16/2002: 51 year old male who had been taking Adderall for approximately 3 years expired in a gym after experiencing a stroke. He had no known relevant past history except for ADHD and was not taking concomitant medications.

Report No: 4151000 MFR No: SUS1-2003-00002: 42 year old male on Adderall XR 15 mg QD X 9 months for ADD with the acute onset of chest pain which rapidly progressed to ventricular fibrillation, asystole and cardiac arrest. Medical history was remarkable for obstructive sleep apnea (weight: 238, height :?), hypertension and dysrhythmia. Concurrent medications included hydrochlorothiazide, quinapril for hypertension.

CSENUM 389811039, MFR No: US0301700U: 19 year old female, straight A, college student, used Adderall without a prescription (dose and duration uncertain) to help her study for final exams. She may have also been taking over the counter diet pills (type, dose, and duration are uncertain), but was on no other medications. She had no history of cardiac problems. She woke up her roommate complaining of chest pain and an inability to breathe, having been well several hours prior to her acute event. She

collapsed and went into arrest for 18 minutes, for which she was defibrillated 2X at the scene and intubated. She was found to have multiple arrhythmias (ventricular tachycardia), be in congestive heart failure, and was diagnosed with biventricular cardiomyopathy (ejection fraction of 20 %). Toxicology screen was positive for amphetamines. The patient remained in a persistent vegetative state requiring a gastrostomy tube and a tracheotomy. Prior to this event the patient had no history of cardiac problems. A cardiac biopsy was performed, but no follow-up information was provided. A follow-up report indicates that the patient died. Same as case No. 4069419, US0301701.

- **Death From Suicide**

CSENUM 3442770 MFR No: US00025: 25 year old male with bipolar disorder and substance abuse was treated with Adderall (dose and duration, unknown) and Effexor (venlafaxine) committed suicide by hanging. The number of remaining Adderall tablets suggested excess use. It is unclear if an autopsy or drug screen were performed.

Summary of Deaths on Adderall in AERS

Eight (8) unexpected, sudden patient (5 M, 4 F; avg: 37.33 yrs) deaths occurred in patients taking Adderall. One (1) additional patient taking Adderall committed suicide. Four (4) of the deaths appeared to be cardiac related, two (2) others were probably cardiac (not definite), and two (2) deaths resulted from strokes. Physical exertion may have been a precipitating factor in two (2) of the patients deaths, and a pre-existing cardiomyopathy with an arrhythmia possibly in conjunction with another drug(s) was a cause in another death. Clearly recognized risk factors were only present in two patients (pre-existing cardiomyopathy with an arrhythmia, and sleep apnea with hypertension). Five (5) of the patients had no clearly recognized risk factor. No information on risk factors was present in two (2) patients. Duration of therapy was 3 years in 2 patients; less than a year in 4 patients (avg 3.87 mths) and no information were present for the other three (3) patients. Information on dosing was present in 4 patients and did not appear to be excessive. Six (6) patients were on concurrent medications, one (1) was on no other medications, and no information was available for two (2) other patients.

Table: Summary of Adults Deaths and Adderall Use: Post-Marketing AERS

Age	Sex	Dose	Duration	Risk Factors	Other Meds	Type	Outcome
25	M	?	?	Bipolar Substance Abuse	Effexor	Suicide (Hanging)	Death
51	M	20 mg TID	3 years	CV (±)	?	Stroke	Death
62	M	10 mg, 5 mg	13 days	Physical Exertion Mild HTN	?	MI	Death
22	F	?	4 mths	None	Wellbutrin	Found Dead	Sudden Death
28	F	?	?	?	Celexa	Flu like sx's Chest Pain	Sudden Death
36	F	5-30 mg BID	2 mths	Adriamycin cardiomyopathy Arrhythmia	Elavil Effexor Methadone Etc.	Cardiac arrest Subarachnoid hemorrhage	Death
51	M	?	3 years	Physical Exertion	None	Stroke	Death
42	M	15 mg QD	9 mths	Sleep apnea, HTN	HCTZ Quinapril	Chest pain Ventricular fibrillation	Sudden Death
19	F	?	?	None	OTC?	Chest pain Cardiac arrest Cardiac Myopathy	Sudden Death
37.33 yrs (Avg)	**F: 4 M: 5**	**Nl: 4 ?: 5**	**3 yrs: (2) 3.87 mths Avg: (4) ?: (3)**	**Physical Exertion (N=2) None: (5) Cardiomyopathy/Arrhythmia (1) Sleep apnea/HTN (1)**	**Yes (6) No (1) ? (2)**		**Sudden (4) Arrhythmia (1) Hypertrophy (1) Heart Disease (1) Stroke (2) Suicide (1**

3. Stroke

CSENUM 3003088, MFR No: 112597A: 51 year old male with ADD on Adderall 20 mg TID X 3 years when he died from a stroke. He may have had a history of cardiovascular problems. No information on the autopsy was provided. Same as Case No. 3004170.

CSENUM 3021480, MFR No: 98030601: 48 year old female with ADHD on Adderall 10-20 mg/ day X 1 year, when she had a mild stroke, for which she recovered. The patient had no history of cardiovascular disease and was otherwise healthy. Same as Case No. 3049195.

CSENUM 3193066, MFR No: 97111702: 30 year old female, previously treated with Dexedrine (dose and duration unknown) was taking Adderall (dose and duration unknown) when she had a stroke resulting in an optic neuropathy. No information on outcome was provided. Same as Case No: 3153954.

CSENUM 3594398, MFR No: US0100400: 39 year old female with ADHD, anxiety and depressive symptoms on Adderall 10-15 mg BID X 9 months when she had a stroke and was hospitalized. No information was provided about the patient's outcome. Laboratory studies: TFT's, metabolic panel, CBC; ECG, were all normal prior to beginning Adderall therapy. Same as Case No. 3646707.

CSENUM 3798629, MFR No: US0212200 (?): 19 year old male with ADD on Adderall (20 mg/d, avg.) X 5-6 years, with 10 mth medication hiatus, followed by restarting Adderall (20-30 mg/d) for X 5-6 mths, when he developed a severe headache, insomnia, incapacitating tremor/shaking involving his hands (unable to put a label on an envelope) which extended over the next 3 days to involve his entire body. He was seen in an ER where he was found to be tachycardic (HR: 121 bpm), hypertensive (no number given), and have normal laboratory tests (except, an elevated TFT: not specified), and was treated on an outpatient setting with Lopressor (metoprolol) 50 mg and Xanax (alprazolam) 1 mg TID X 1 month. Neurological examination, 4 days later, was remarkable for balance difficulties. MRI of the brain showed "hyperintensities in 2 areas of the brain" and "evidence of lacunae infarcts". An EEG was performed, but it is unclear, from the available information, if it was abnormal. One month after this event the patient reported persistent tremor. The patient was on no other medications at the time of the events.

CSENUM 3916667, MFR No: US0303500:50 year old female on Adderall 20 mg QD X 7 months for difficulty focusing, suddenly developed left sided weakness while shopping. She was found to have a mild lacunar stroke. Past medical history was remarkable for hypertension, depression, and Type A personality. Concurrent medications included Atenolol 10 mg QD and Norvasc (amidodipine) 10 mg (PRN with SBP > 140), spironolactone 75 mg BID and Aggrenox 25 mg BID. Same as Case No. 4070969.

CSENUM 4133727, MFR No: SUS1-2003-00069: 26 year old female on Adderall 20 mg (duration, unknown) when she developed a stroke. Past medical history was normal and the patient had no history of cardiovascular diseases. Laboratory studies (not listed) were reported as normal. No information was provided about concomitant medications. No follow-up information was provided on the patient.

CSENUM 3919502, MFR No: US0303900: 36 year old female on Adderall XR X 2 months (5 mg to 30 mg BID) to enhance the effects of pain medications developed nausea, stomach pain and fatigue and went into a cardiac arrest X 30 minutes following resuscitation efforts. She developed an anoxic encephalopathy, placed on a ventilator, and was subsequently removed. She was found to have a small subarachnoid hemorrhage. Death was attributed to a combination of Adderall and Elavil with a know cardiomyopathy. Past medical history was remarkable for a history of osteosarcoma at age 15 years;

Adriamycin (doxorubicin) induced cardiomyopathy; severe tachycardia, possibly the result of an accessory pathway; severe depression with 2 prior suicide attempts. Concurrent medications included: Elavil (amitriptyline) 200 mg HS, Toradol (Ketorolac tromethamine) injectable 30 mg BID QOD, Toradol 10 mg QID, Effexor XR (venlafaxine) 200 mg, Ativan (lorazepam) 2 mg QID and methadone 10 mg QD. Same as Case No. 4074653.

CSENUM 3923583, MFR No: US0307500: Male child (age uncertain) on Adderall XR 5 mg (duration uncertain) developed facial paralysis diagnosed as a Bell's palsy. No other information was provided.

Table: Summary of Strokes with Adderall Use: Post-Marketing AERS

Age	Sex	Dose	Duration	Risk Factors	Other Meds	Type	Outcome
51	M	20 mg TID	3 years	CV (±)	None	Unknown	Death
48	F	10-20 mg/d	1 year	None	None	Unknown	Recovered
30	F	?	?	Prior Tx With Dexedrine	?	Unknown	
39	F	10-15 mg BID	9 months	Anxiety (RRF)	None	Unknown	
19	M	20 mg/d	5-6 years	None	None	Lacunae	Persistent tremor
50	F	20 mg/d	7 months	HTN, Type A Personality (RRF)	Yes	Lacunae	
26	F	20 mg (?)	?	None	?	?	
36	F	5-30 mg BID	2 months	Adriamycin cardiomyopathy, possible arrhythmia	Yes	Subarachnoid hemorrhage	Death
37.4 yrs (Avg)	**2 M 6 F**	**Nl (7) ? (1)**	**37.92 mths (3) < 1 yr (3) ? (2)**	**None (5) Cardiomyopathy/Arrhythmia (1) HTN (1)**	**Yes (2) No (4) ? (2)**		**Lacunes (2) Subarachnoid (1)**
CV= Cardiovascular; HTN=Hypertension; (±) = Possibly; RRF=Relative Risk Factor							

Summary of Post-Marketing Cases Involving Stroke:
Eight (8) adult patients (2 M, 6 F; avg: 37. 4 yrs) with strokes were identified from the post marketing AER's database. Females were more frequently affected than males (3:1). Five (5) patients had no clearly identifiable risk factors. Two (2) patients had clearly identifiable risk factors: hypertension (N=1) and a pre-existing cardiomyopathy with possible arrhythmia (N=1). Four (4) of the patients were not taking concurrent medications. Two (2) of the patients were taking were taking concurrent medications [anti-hypertensive(s), N=1; mixed, anti-depressants and narcotics, N=1)]. No information on concurrent medications was available in the other two (2) patients. Information on dosing was present in seven (7) patients and did not appear to be excessive. Duration of therapy was from 1-6 years in the 2 patients without clear risk factors, and in 1 patient with possible cardiovascular risk factors. Duration of therapy was shorter in the 2 patients with definable risk factors. No information on therapy duration was available in 2 patients. Information on the types of strokes that the patients were available for three (3) cases: lacunae's occurred in 2 patients, and a subarachnoid hemorrhage occurred in 1 case. It is not clear that the subarachnoid hemorrhage was related to the cause of death.

Comment: A review of the literature identified two (2) cases of pediatric stroke secondary to cerebral vasculitis from long-term (1.5 to 7 years), normal dose (20 mg/day) of methylphenidate (MPH) use. Despite extensive work-ups in these cases, no other explanation was identifiable.

Trugman[65] describes an 18 year old male with a past history of hyperactivity and behavioral problems, treated with methyl-phenidate (MPH) (10 mg BID) for 7 years and whom presented at 12 years of age with intermittent headaches for several months followed by the sudden onset of right hemiparesis and aphasia. On the day of admission, he was normotensive with a CCT scan of the head showing no hemorrhage. A cerebral angiogram, done the next day, showed an occlusion of the left anterior cerebral artery and posterior branch of the left middle cerebral artery, and irregularity of the proximal left middle cerebral artery. These findings suggested arteritis. After an extensive work-up which determined no other etiology it was concluded that the cerebral arteritis and infarction were caused by chronic oral MPH use. In the 6 years since, the stroke, "the patient stopped taking MPH and he has had no evidence of active CNS system or systemic vasculitis".

Schteinschnaider ET. AL[66], describes an 8 year old male with a past history of hyperactivity and behavioral problems, treated with methylphenidate (MPH) (20 mg QD) for 1.5 years who developed the sudden onset of left upper extremity paresthesia

65 Trugman JM. Cerebral arteritis and oral methylphenidate. Lancet. 1988 Mar 12; 1(8585):584-5.

66 Schteinschnaider A, Plaghos LL, Garbugino S, Riveros D, Lazarowski A, Intruvini S, Massaro M. Cerebral arteritis following methylphenidate use. J Child Neurol. 2000 Apr; 15(4):265-7

which resolved. Two (2) months later he had another, but more intense episode "that extended to the homolateral hemiface and he developed functional impotence of the arm that expanded to the whole hemibody 48 hours later." The episode resolved in 24 hours. He was then symptom free until 2 months later, when he experienced a third, more intense episode than his previous ones that left him with sequels: "ataxia, dysmetria in the left hemibody, and dystonic movements of the left upper limb." CCT scan showed a hypodense area in the left thalamic region. MRI showed multiple, bi-thalamic, non-enhancing areas. Cerebral angiogram showed enlargement of the basilar artery and proximal segments of both posterior cerebral arteries. Distal bilateral complete occlusions with collateral circulation through pial anastomosis were observed. These images were diagnosed as being compatible with localized vasculitis. An extensive work-up to identify causes for the cerebral vasculitis was unrevealing. The author concluded that based on the "the absence of new symptoms after interrupting the ingestion of MPH, the negative family history, the exclusion of other cause of vasculitis suggest a causal relation between MPH ingestion and development of cerebral arteritis."

Amphetamines have also been implicated in the etiology of cerebral vasculitis and stroke. It was first described in drug abusers and was though to be related to intravenous administration of methamphetamine[67]. It can produce angiographic changes consisting of decreased vessel caliber and absence of filling in small middle cerebral artery branches.

4. Myocardial Infarctions

CSENUM 3206763, MFR No: US9908800: 62 year old male with ADD on Adderall (10 mg AM, 5 mg PM) X 13 days had a MI while shoveling snow. The patient was last seen by his physician 2 weeks prior to the event and he did not have any active co-morbid health conditions, except for mild hypertension (155/95) and a weight of 210 lbs (height not available). Past medical history was remarkable for a history of alcoholism 9 years prior and poor dietary habits (?). No information on an autopsy was provided.

CSENUM 3545941, MFR No: US0015100: 45 year old female with ADD and migraines, on Adderall 30 mg BID and Wellbutrin (Bupropion), nefazodone, divalproxex and metoprolol, developed chest pain, found to have a non-Q wave MI, and was hospitalized. Work-up during her hospitalization showed an ejection fraction of 60 % and a normal cardiac catherization. Past medical history was remarkable for a cardiac arrhythmia. The patient recovered. Same as Case No. 3584640.

67 Perez JA Jr, Arsura EL, Strategos S. Methamphetamine-related stroke: four cases. J Emerg Med. 1999 May-Jun; 17(3):469-71.

CSENUM 3846324, MFR No: US0218300: 28 year old male on Adderall 20 mg TID X 2 days for narcolepsy when he developed episodes of chest pain associated with dizziness over several weeks. An ECG was performed at his physician's office which revealed ECG changes. Cardiac monitoring showed a HR of 140-150. A cardiac catheterization was planned. The patient had no history of cardiac problems and no other medical conditions. He was not taking any other medications. The chest pain stopped when the Adderall stopped. Same as Case No. 3982857.

CSENUM 3776399, MFR No: US0118900: Male patient (age, unknown) on Adderall (duration and dose, unknown) had a myocardial infarction. Past medical history was remarkable for a prior myocardial infarction. The patient was said to be under significant stress at the time of the event.

Report No: 3667095 MFR No: US0102100: 21 year old male on Adderall (dose and duration, uncertain) took 3 capsules of Thermadrine (an OTC product, containing 300 mg Ephedra), one hour prior to working out and had a myocardial infarction. No other information or follow-up was provided.

Report No: 3821633 MFR No: US0127500: 57 year old male on Adderall X 3 years for depression had chest pain, found to have a myocardial infarction, and was hospitalized. A cardiac catheterization was performed, but, no results are given in the report. Adderall was stopped and he was placed on a beta blocker. He suffered a second myocardial infarction, 4 months later. Concurrent medications with Adderall consisted of Vioxx (rofecoxib). Past medical history consisted of bilateral prosthetic hip replacements. Family history consisted of a father who died of a heart attack at a young age.

Table: Summary of Myocardial Infarction (MI) and Adult Adderall Use: Post-Marketing AERS

Age	Sex	Dose	Duration	Risk Factors	Other Meds	Type	Outcome
62	M	10 mg, 5 mg	13 days	Mild HTN Physical Exertion	None	?	Death
45	F	30 mg BID	?	Migraines (RRF) Arrhythmia	Yes	Nl vessels	?
28	M	20 mg TID	2 days	None Narcolepsy (RRF)	None	?	?
?	M	?	?	Previous MI Stress (RRF)	?	?	?
21	M	?	?	Physical Exertion	Ephedra	?	?
57	M	?	3 years	FHX MI	?	?	Recurrent
42.6 yrs (Avg)	**F: 1 M: 5**	**Nl (3) ? (3)**	**3 yrs (1) < 0.5 mth (2) ? (3)**	**Physical Exertion (2) Previous MI (1) Arrhythmia (1) FHX MI (1)**	**No (2) Yes (2) ? (2)**	**Vessels Nl (1)**	**Death (1) Recurrent (1) ? (4)**
MI= Myocardial Infarction; HTN=Hypertension; RRF=Relative Risk Factor							

Summary of Post-Marketing Cases Involving Myocardial Infarctions:
Six (6) adults patients (5 M, 1 F; avg: 42. 6 yrs) with MI's were identified from the postmaketing AER's database. Males were more frequently affected than females (5:1). Two (2) cases were precipitated by physical exertion. Identifiable cardiac risk factors consisted of previous MI (N=1), an arrhythmia (N=1), and a family history of early MI (N=1) [note: some patients had more than one risk factor]. Two persons had non-cardiac, perhaps, relative risk factors. One person had mild HTN (N=1) and another had migraines. Duration of therapy was uncertain in three (3) patients, 2 days in one (1) patient, 13 days in one patient and 3 years in one patient. Two patients were on other medications at the time of the MI. Angiographic information was available on only one (1) patient and showed normal coronary vessels.

Comment: A review of the literature identified a patient on amphetamine Costa ET. AL.[68] described a 34 year old male on amphetamine therapy for 1 week for weight loss when he developed chest pain and which based on ECG changes, echocardiography and CK levels was diagnosed as an acute, inferior left ventricular, myocardial infarction. His only risk factor was cigarette smoking (1 PPD). Coronary angiograms were normal. The author reviewed the literature and identified 9 other cases of myocardial infarction associated with amphetamine use or abuse. Four (4) of the nine cases resulted from oral use. The duration of amphetamine use prior to symptom onset varied from a few minutes to years. One patient[69], a 31 year old body builder, was on other drugs (steroids, potassium, frumil) when he collapsed with a myocardial infarction and ventricular tachycardia. The others were on no other medications.

5. Other Cardiac Events

- **Arrhythmias, Not Resulting in Death**

CSENUM 3504647, MFR No: US0011001: 40 year old male, runner with ADD, on Adderall 20 mg/day (BID) x 2 years, went out to run at noon at the Mayo clinic where he worked. Upon returning from his run, he complained to co-workers of not feeling well and he collapsed. Immediate emergency care was started. He went into ventricular fibrillation, progressing to a full cardiac arrest wit successful resuscitation. Post cardiac arrest tests (ECG, echocardiogram and angiogram) were all normal. Neither the patient nor his family had a history of cardiac problems. The patient recovered. Same as Cases: 3526409 and 3532719.

CSENUM 3526409, MFR No: US0011000: Adult male (age uncertain) on Adderall (dose and duration of treatment is uncertain) with no history of cardiac disease experienced atrial fibrillation and cardiac arrest with full recovery. No other information was provided.

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68 Costa GM, Pizzi C, Bresciani B, Tumscitz C, Gentile M, Bugiardini R. Acute myocardial infarction caused by amphetamines: a case report and review of the literature. Ital Heart J. 2001 Jun;2(6):478-80.

69 Appleby M, Fisher M, Martin M. Myocardial infarction, hyperkalaemia and ventricular tachycardia in a young male body-builder. Int J Cardiol. 1994 Apr;44(2):171-4.

CSENUM 3731376, MFR No: US0112900: 19 year old female with ADD on Adderall (15 mg AM, 15 mg noon) X 4 years. Diagnosed with Wolff-Parkinson-White syndrome, Mahiam fibers, and treated with an ablative procedure 1 year prior to event. She developed chest pain and "inflammation around the heart." Symptoms persisted with discontinuation of the Adderall.

CSENUM 3972575, MFR No: SUS1-2003-00139: Male patient (age uncertain) on Adderall XR (dose and duration, uncertain) was admitted to a hospital because of shortness of breath and chest pain. Past medical history was remarkable for and a myocardial infarction 5 years prior to the current event. The patient was having premature ventricular contractions at the time of the current event. No other information was provided.

Report No: 4144170 MFR No: SUS1-2003-00131: 56 year old male on Adderall XR (dose and duration, uncertain) for adult ADHD developed an atrial arrhythmia (supraventricular arrhythmia) requiring required cardioconversion. He had no history of a heart condition. There is no information on concomitant medications.

Report No: 4148227 MFR No: SUS1-2003-00017: 54 year old male on Adderall 15 mg QD (duration uncertain) for ADHD had a syncopal spell and subsequently developed supraventricular tachycardia. Medical history was remarkable for a pacemaker (placed 9 months prior to the event) and osteoarthritis. Concurrent medications included: aspirin (PRN), celecoxib (PRN) and tramadol (PRN).

Table: Summary of Arrhythmia and Adult Adderall Use (Non-Death): Post-Marketing AERS

Age	Sex	Dose	Duration	Risk Factors	Other Meds	Type	Outcome
40	M	20 mg BID	2 years	Physical Exertion	None	Nl vessels	Ventricular Fibrillation Arrest
?	M	?	?	None	?	?	Atrial Fibrillation Arrest
19	F	15 mg BID	4 years	WPW Syndrome	?	?	CP "inflammation around the heart"
?	M	?	?	Previous MI	?	Chest Pain Shortness of Breath	PVC's
56	M	?	?	None	?	Atrial (Supraventricular) Arrhythmia	Cardioconversion
54	M	15 mg QD	?	Pacemaker	ASA Celecoxib Tramadol	Syncopal Spell Supraventricular Tachycardia	
42.25 yrs (Avg)	M: 5 F: 1	Nl: 3 ?: 3	3 yrs: 2 ?: 4	None: 3 Previous Cardiac: 3 Physical Exertion: 1	Yes (1) No (1) ? (4)	Vessels Nl (1) Inflammation around heart" (1) SVT's (2) PVC's (1	Arrest (2) Cardioversion (1)

Summary of Adult Post-Marketing Cases Involving Arrhythmias Not Leading to Death:
Six (6) adults patients (5 M, 1 F; avg: 42.25 yrs) with arrhythmias which did not result in death were identified from the postmaketing AER's database. Males were more frequently affected than females. One (1) case was precipitated by physical exertion. Three (3) patients had no identifiable risk factors. Identifiable risk factors in the other three (3) patients consisted of a pre-existing arrhythmia (N=1), a cardiac problem as evidenced by a pacemaker (N=1) and history of a previous MI (N=1). Duration of therapy was uncertain in four (4) patients, and 3 years (average) in the other two (2) patients. Information on concomitant medications was unavailable for four (4) medications. Of the other two (2) patients, one was on concomitant medications and the other was on no medications. Coronary angiography on one (1) patient showed normal cardiac vessels.

Table: Summary of Arrhythmia and Adderall Use (Non-Death and Probable Cause of Death): Post-Marketing AERS

Age	Sex	Dose	Duration	Risk Factors	Other Meds	Type	Outcome
40	M	20 mg BID	2 years	Physical Exertion	None	Nl vessels	Ventricular Fibrillation Arrest
?	M	?	?	None	?	?	Atrial Fibrillation Arrest
19	F	15 mg BID	4 years	WPW Syndrome	?	?	CP "inflammation around the heart"
?	M	?	?	Previous MI	?	Chest Pain Shortness of Breath	PVC's
56	M	?	?	None	?	Atrial (Supraventricular) Arrhythmia	Cardioconversion
54	M	15 mg QD	?	Pacemaker	ASA Celecoxib Tramadol	Syncopal Spell Supraventricular Tachycardia	
42	M	15 mg QD	9 mths	Sleep apnea, HTN	HCTZ Quinapril	Chest pain Ventricular fibrillation	Sudden Death
11	M	20 mg IR Generic (1 dose)	? "some time"	Physical Exertion	?	Collapsed during activities at camp Arrhythmia Amphetamine Toxicity with normal use	Sudden Death
7	M	?	?	Heart murmur	?	Bicuspid aortic valve Arrhythmia	Sudden death in sleep
13	M	20 mg	1 dose	Idiopathic Hypertrophic Subaortic Stenosis (IHSS)	None	Athletic child who collapsed and died after dosing IHSS Arrhythmia	Sudden Death
14	M	?	3 years	Physical Exertion Heart murmur (RRF)	None	Arrhythmia Cardiac Hypertrophy From Chronic Amphetamine	Sudden Death

15	M	20 mg	3 years	Physical Exertion Resolved heart murmur (RRF)	None	Arrhythmia Increased " heart density"	Sudden Death
12	M	Ritalin (dose?) 10 mg (XR)	4 yrs 1 dose	Physical Exertion Arrhythmia-Mother (RRF)	None	Collapsed while running cross country	Sudden Death
25.72 (Avg)	**M: 12** **F: 1**	**Nl: 8** **?: 5**	**38.4 mths: 5** **9 mths: 1** **1 dose: 1** **?: 6**	**Physical Exertion: 5** **Previous Cardiac: 3** **Sleep Apnea: 1** **Heart Murmurs: 2** **Occult Heart 1:** **None: 2**	**None: 5** **Meds: 2** **?: 6**	**Vessels Nl (1)** **Hypertrophy (2)** **IHSS (1)** **Abn. Valve (1)** **SVT (2)** **VFib (1)**	**Sudden Death (7)** **Resuscitation (2)** **Cardioversion (1)**

Summary of Adult Post-Marketing Cases Involving Arrhythmias (Non-Death & Probable Cause of Death): Thirteen (13) patients (12 M, 1 F; 7-56 yrs, avg: 25.72 yrs) with arrhythmias, as determined by clinical history or autopsy were identified from the postmaketing AER's database. Males were more frequently affected than females. Five (5) cases were precipitated by physical exertion. Six (6) patients had no identifiable risk factors. Identifiable risk factors in three (3) patients consisted of previous cardiac problems: a pre-existing arrhythmia (N=1), a cardiac problem as evidenced by a pacemaker (N=1) and a history of a previous MI (N=1). Two (2) other patients had heart murmurs. One patient had unrecognized heart disease (Idiopathic Hypertrophic Subaortic Stenosis). Duration of therapy was 38.4 mths for 6 patients, 9 mths for 1 patient, and 1 dose for 1 patient. No information on duration of therapy was available for six (6) patients. Five (5) patients were on no concurrent medications and two (2) were on concurrent medications. Information on concurrent medications was unavailable for six (6) patients.

Table: Summary of Arrhythmia and Adderall Use (Non-Death and Probable\ Possible Cause of Death): Post-Marketing AERS

Age	Sex	Dose	Duration	Risk Factors	Other Meds	Type	Outcome
40	M	20 mg BID	2 years	Physical Exertion	None	Nl vessels	Ventricular Fibrillation Arrest
?	M	?	?	None	?	?	Atrial Fibrillation Arrest
19	F	15 mg BID	4 years	WPW Syndrome	?	?	CP "inflammation around the heart"
?	M	?	?	Previous MI	?	Chest Pain Shortness of Breath	PVC's
56	M	?	?	None	?	Atrial (Supraventricular) Arrhythmia	Cardioconversion
54	M	15 mg QD	?	Pacemaker	ASA Celecoxib Tramadol	Syncopal Spell Supraventricular Tachycardia	
42	M	15 mg QD	9 mths	Sleep apnea, HTN	HCTZ Quinapril	Chest pain Ventricular fibrillation	Sudden Death
11	M	20 mg IR Generic (1 dose)	? "some time"	Physical Exertion	?	Collapsed during activities at camp Arrhythmia Amphetamine Toxicity with normal use	Sudden Death
7	M	?	?	Heart murmur	?	Bicuspid aortic valve Arrhythmia	Sudden death in sleep
13	M	20 mg	1 dose	Idiopathic Hypertrophic Subaortic Stenosis (IHSS)	None	Athletic child who collapsed and died after dosing IHSS Arrhythmia	Sudden Death
14	M	?	3 years	Physical Exertion Heart murmur (RRF)	None	Arrhythmia Cardiac Hypertrophy From Chronic Amphetamine	Sudden Death
15	M	20 mg	3 years	Physical Exertion	None	Arrhythmia	Sudden Death

				Resolved heart murmur (RRF)		Increased " heart density"	
12	M	Ritalin (dose?) 10 mg (XR)	4 yrs 1 dose	Physical Exertion Arrhythmia-Mother (RRF)	None	Collapsed while running cross country	Sudden Death
16	M	?	2 years	?	Zyprexa	Hepatic steatosis	Found dead next to bed
11	M	10 mg BID	4 yrs	IDDM	Insulin	Amphetamine toxicity	Sudden death in sleep ? Suicide
10	M	?	8 yrs bb	Physical Exertion	?	Died during sports	Sudden Death
10	M	10 mg BID	6 mths	Physical Exertion	None	Athletic child who died while swimming in shallow water	Sudden Death?
15	M	20 mg	18 mths	?	None	Autopsy normal except for tissue neurtropenia.	Sudden Death
19	F	?	?	None	OTC?	Chest pain Cardiac arrest Cardiomyopathy	Death
22	F	?	4 mths	None	Wellbutrin	?	Found Dead
28	F	?	?	?	Celexa	Flu like sx's Chest Pain	Sudden Death
21.78 yrs (Avg)	**F: 4 M: 17**	**Nl: 11 ?: 10**	**42 mths: 9 6.3 mths: 3 1 dose: 1 ?: 8**	**None: 4 Physical Exertion: 7 Previous Cardiac: 3 Sleep Apnea: 1 Heart Murmurs: 2 Occult Heart: 1**	**None: 7 Meds: 7 ?: 7**	**Vessels Nl (1) Hypertrophy (2) Cardiomyopathy (1) IHSS (1) Abn. Valve (1) SVT (2) VFib (1)**	**Sudden Death (14) Resuscitation (2) Cardioversion (1)**

Summary of Adult Post-Marketing Cases Involving Arrhythmias (Non-Death & Probable/Possible Cause of Death): **(Non-Death and Death, Probable Cause):**
Twenty-one (21) patients (17 M, 4 F; 7-56 yrs, avg: 21.78 yrs) with arrhythmias, as determined by clinical history, autopsy; or the sudden, inexplicability of the event (*possible*) were identified from the postmaketing AER's database. Males were more frequently affected than females. Seven (7) cases were precipitated by physical exertion. Thirteen (13) patients had no identifiable risk factors. Identifiable risk factors in three (3) patients consisted of previous cardiac problems: a pre-existing arrhythmia (N=1), a cardiac problem as evidenced by a pacemaker (N=1) and a history of a previous MI (N=1). Two (2) other patients had heart murmurs. One patient had unrecognized heart disease (Idiopathic Hypertrophic Subaortic Stenosis). Another patient had sleep apnea and hypertension, potential risk factors because of sleep apneas association with arrhythmias and autonomic dysfunction. Average duration of therapy was 42 mths for 9 patients, 6.3 mths for 3 patients and 1 dose for 1 patient. No information on duration of therapy was available for eight (8) patients. Seven (7) patients were on no concurrent medications and seven (7) were on concurrent medications. Information on concurrent medications was unavailable for seven (7) patients.

- **Cardiomyopathy**

CSENUM 4033761, MFR No: US0223300: Adult male with ADD on Adderall (40-80 mg/day) X 2 years when he developed chest pain, coughing and vomiting which were diagnosed as being secondary to heart failure, and for which the patient required a cardiac transplantation. (b) (6) (b) (6) ".

Report No: 1889272 MFR No: 022697A: 17 year old male on Adderall 20 mg (duration uncertain) for an uncertain reason was hospitalized because of dyspnea, hypoxia, hypotension and found to have a cardiomyopathy. Concomitant drugs included cannabis and pseudoephedrine.

Report No: 3667094 MFR No: US0100700: 43 year old male on Ritalin 20 mg BID X 2.5 years for ADD, inadvertently switched to Adderall 20 mg BID. After 1 day developed chest pain, shortness of breath. He was taken to the hospital where he was hypertensive (180/110 from baseline of 90/60), had EKG change and had an ejection fraction of 35 %. Cardiac catheterization showed clear arteries and he was diagnosed as having a non-ischemic, cardiomyopathy, and he became a possible cardiac transplant candidate. The patient was found to have developed mild left sided weakness presumably secondary to a "very mild stroke." Concurrent medication at the time of the event consisted of Percocet 1 tablet BID (PRN).

CSENUM 3919502, MFR No: US0303900: 36 year old female on Adderall XR X 2 months (5 mg to 30 mg BID) to enhance the effects of pain medications developed nausea, stomach pain and fatigue and went into a cardiac arrest X 30 minutes following resuscitation efforts. She developed an anoxic encephalopathy, placed on a ventilator, and was subsequently removed. She was found to have a small subarachnoid hemorrhage. Death was attributed to a combination of Adderall and Elavil with a know cardiomyopathy. Past medical history was remarkable for a history of osteosarcoma at age 15 years; Adriamycin (doxorubicin) induced cardiomyopathy; severe tachycardia, possibly the result of an accessory pathway; severe depression with 2 prior suicide attempts. Concurrent medications included: Elavil (amitriptyline) 200 mg HS, Toradol (Ketorolac tromethamine) injectable 30 mg BID QOD, Toradol 10 mg QID, Effexor XR (venlafaxine) 200 mg, Ativan (lorazepam) 2 mg QID and methadone 10 mg QD. Same as Case No. 4074653.

Table: Summary of Cardiomyopathy and Adderall Use: Post-Marketing AERS

Age	Sex	Dose	Duration	Risk Factors	Other Meds	Type	Outcome
?	M	40-80 mg/d	2 years	?	?	Cardiomyopathy	Heart Transplant?
17	M	20 mg	?	?	Yes (PRN)	Cardiomyopathy	
43	M	Ritalin 20 mg BID Then, Adderall 20 mg BID	2.5 years 1 day	?	Yes (PRN)	Nl arteries Non-ischemic cardiomyopathy	CVA Heart Transplant?
19	F	?	?	None	OTC Diet (?)	Ventricular Tachycardia Cardiomyopathy	Death
36	F	5-30 mg	2 mths	Adriamycin cardiomyopathy Arrhythmia	Yes	?	Death
28.75 yrs (Avg)	F: 2 M: 3	High: 1 Nl: 3 ?: 1	2.25 yrs (2) 2 mth (1) ? (2)	Adriamycin cardiomyopathy w/ Arrhythmia (1) No (1) ? (3)	Yes (3-4) ? (1)	Arteries: Nl (1)	Heart Transplant (2 ?) Stroke (1) Death (2) ?: 1

Summary of Post-Marketing Cases Involving Cardiomyopathy:
Five (5) adult patients (3 M, 2 F; avg: 28.75 yrs) with cardiomyopathy were identified from the postmaketing AER's database. One patient had pre-existing cardiomyopathy related to treatment with adriamycin years earlier, and this may have been contributory to her death. No identifiable risk factors were present for one (1) patient, and no risk factors were reported for the other three (3) patients. At times the dosing may have been high in one patient but normal in the others. No information on dosing was available in one patient. Duration of therapy was uncertain in two (2) patients, greater than 2 years in two (2) patients (one with a different stimulant for part of that time), and 2 months in the patient with the adriamycin cardiomyopathy.

6. Hypertension

CSENUM 3923597, MFR No: US0308299: 13 year old child (sex not specified) was on Adderall XR 10 mg (duration uncertain) and developed severe hypertension (200/110) and was admitted to the ICU. No follow-up information was provided.

CSENUM 3494282 MFR No: US9915600: 53 year old male on Adderall XR 10 mg QD X 2 weeks for ADD and Fluoxetine X 1 month, developed borderline hypertension (150/90) several hours post-Adderall XR dosing.

CSENUM 3494258 MFR No: US9918000: 18 year old, athletically active, male on Adderall 10-20 mg X 2 weeks and developed borderline hypertension (110/60-70 to 130/85).

CSENUM 3237222 MFR No: US98063:41 year old female on Adderall 20 mg BID X 6 days for ADD developed palpitations, hypertension, facial tic and gastrointestinal reflux disease. Adderall was discontinued but the patient's blood pressure remained somewhat elevated.

CSENUM 3818237 MFR No: US0214900: Adult male (age uncertain) with pre-existing Type II diabetes and borderline hypertension was started on Adderall 10 mg X 2 weeks for uncertain reason. On the Adderall, he developed hyperglycemia (160-170), hypertension (140/85 to 164/94) and an increased heart rate (80 to 92). Concurrent medications included Glucotrol XL (glipizide), Glucophage (metformin) and Monopril (fosinopril).

7. Ischemic Bowel Disease

Report No: 3642748 MFR No: US 0022900: 19 year old female on Adderall 15 mg BID X 3 years for ADHD and developed abdominal pain and rectal bleeding. She was diagnosed as having ischemic colitis and required a colostomy. Past medical history was remarkable for insulin controlled diabetes. Since her surgery the patient's diabetes has been difficult to control and she has required anti-coagulation therapy.

Table: Summary of Ischemic Bowel Disease and Adderall Use: Post-marketing AERS

Age	Sex	Dose	Duration	Risk Factors	Other Meds	Type	Outcome
19	1 F	15 mg BID	3 years	IDDM	Yes (1)	No	Colostomy Worse DM Control

Comment: A review of the literature identified one(1) case[70] of a 42 year old male who developed methamphetamine induced ischemic colitis 2 days following recreational use.

8. Vasomotor Instability

CSENUM 3237219 MFR No: US98062:35 year old female on Adderall 10 mg BID for ADD X 3-4 months who developed Raynaud's like symptoms (blue and cold fingers, 3 hours post dosing, and with cold exposure and exacerbated by cigarette smoking). The patient is on no other medications. Diagnostic work-up consisting of EKG, chest X-ray and various laboratory studies were reportedly normal.

CSENUM 3494258 MFR No: US9914700: 25 year old female on Adderall 20 mg QD X 1 day and developed a red, itchy and hot face.

Report No: 3522742 MFR No: US9914500: 25 year old female on Obetrol (dose and duration, uncertain) for ADHD developed vasodilatation. No other information was provided.

Report No: 3522718 MFR No: US9911900: Adult (age uncertain) male patient on Adderall 10 mg (duration, uncertain) for ADHD developed vasospasm. No other information was provided.

Report No: 3230131 MFR No: US98062: 35 year old female on Adderall (dose and duration uncertain) for ADHD developed vasodilatation and vasospasm. No further details are provided.

Report No: 3522719 MFR No: US9912000: 35 year old female on Adderall 10 mg (duration uncertain) for ADHD developed cold toes with sores, and painful in an extremity. Concurrent medications included naprosyn and levathyroid.

Report No: 4081997 MFR No: US0307100: 46 year old female on Adderall X 3 months (dose uncertain) for ADD, developed episodes of acute burning on a toe in her foot lasting 10 minutes and returning a few hours to days later. One week later she developed redness at the bottom of her toe. This was followed by the development of the same thing in the toes of her other foot and possible swelling of her hands. An angiogram was performed which showed not good flow to her toes. Work-up was negative for vasculitis. It appears that she developed thrombosis of 3 toes. She was treated with IV heparin and switched to coumadin (warfarin) and Lovenox. She also developed blurring of her vision. Concurrent medications consisted of a performance enhancer ("Parrillo Performance") which contained primrose oil, vitamins, amino acids, electrolytes and an endurance formula (?).

70 Dirkx CA, Gerscovich EO. Sonographic findings in methamphetamine-induced ischemic colitis. J Clin Ultrasound. 1998 Nov-Dec; 26(9):479-82.

Table: Summary of Vasomotor Instability and Adderall Use: Post-marketing AERS

Age	Sex	Dose	Duration	Risk Factors	Other Meds	Type	Outcome
35	F	10 mg BID	3-4 mths	Cigarettes	None		Cyanotic hands
25	F	20 mg QD	1 day	?	?		Red, hot face
25	F	?	?	?	?		Vasodilatation
?	M	10 mg	?	?	?		Vasospasm
35	F	?	?	?	?		Vasodilatation Vasospasm
35	F	10 mg	?	Hypothyroid	Yes		Cold toes + sores Painful extremity
46	F	?	3 mths	?	Yes (OTC)	Angiogram: poor blood flow to toes	Redness toes Thrombosis of toes
33.5 yrs (Avg)	1 M 6 F	Nl: 4 ?: 3	< 4 mth (3) ? (4)	None: 2 ?: 5	Yes: 2 No: 1 ?: 4	Angiogram: Abn	Cyanotic Extremities (3) Thrombosis toes (1)

Summary of Post-Marketing Cases Involving Vasomotor Instability:
Seven (7) adult patients (1 M, 6 F; avg: 33. 5 yrs) with presumptive vasomotor instability were identified from the AER's database. In three (3) patients the event was described as vasospasm or vasodilatation and, there was little to no other information available to further characterize the adverse event. Three (3) patients had cyanotic extremities, two (2) of which involved both the feet and hands, and one (1) of which, involved only the hands. Vascular compromise was present in two (2) patients: one (1) patient, as evidenced by skin sores; and in one (1) patient, as evidenced by angiographic documentation of distal thrombosis. Patient dosing was normal for four (4) patients. No information was provided for three (3) patients. Duration of treatment was less than 4 months for three (3) patients, and unknown for four (4) patients. Two (2) patients were using concomitant medications and one (1) patient was on no other medications. Information on concomitant medications was unavailable for four (4) patients. No clearly associated risk factors were present in two (2) patients, and no information was available for five (5) patients. An angiogram was performed on one patient and showed poor blood flow to the toes.

6. Summary of Critical Safety Findings and Limitations of Data

The most frequently occurring events in Study 303 were dry mouth (drug: 35.1%; placebo: 4.7 %), anorexia (drug: 33%; placebo: 3.1 %), insomnia (drug: 27.2 %; placebo: 12.5 %), headache (drug: 26.2%; placebo: 12.5 %), nervousness (drug: 12.6%; placebo: 12.5 %), and weight loss (drug: 10.5%; placebo: 0 %). Other events occurring more frequently in subjects on drug in Study 303 were: anxiety (drug: 7.9%; placebo: 4.7 %), agitation (drug: 7.9%; placebo: 4.7 %), dizziness (drug: 7.3%; placebo: 0 %), palpitations (drug: 4.2%; placebo: 0 %), tachycardia (drug: 6.3%; placebo: 3.1%), diarrhea (drug: 6.3%; placebo: 0 %) and nausea (drug: 8.4%; placebo: 3.1%).

In studies 303 and 304, individual adverse events, potentially be of concern included suicidality with bipolar psychosis, left upper extremity weakness with headache, reduction in visual acuity (amblyopia), manic reaction, onset or worsening of hypertension, tachycardia, dizziness with heart block, dizziness, amnesia or forgetfulness, speech disorder (stuttering) with worsening of concentration and tremors, foggy and abnormal thinking, chest pain with headaches, chest pain with weakness, dyspnea with pain radiation to left arm, bilateral hand numbness, QT prolongation, dyspnea with cold hands, etc.

Anxiety and depression (HAM-A, HAM-D) essentially worsened with the 40 mg and 60 mg doses in study 303 and with increased duration in study 304. More subjects were developing nervousness (20.6 %) and depression as adverse events (6.7 %) in study 304. The actual percentage of subjects with nervousness may have been greater, since anxiety was coded as a separate adverse event (9.4 %), meaning that as many as 30 % of subjects developed

anxiety-nervousness. Some cases coded as asthenia (8.1 %) could have also been conceivably depressed.

The 40 mg group showed the largest increases in SBP at week 4 [5.9 (p=0.000)], largest increases in DBP at week 3 [2.3 (p=0.054)] and largest increases in pulse at week 3 [8.8 (p=0.002)].

More treatment emergent ECG abnormalities occurred in subjects treated with Adderall XR.

The impact of many of these adverse events [e.g. increased depression and anxiety; anorexia (33%), insomnia (27.2 %), headache (26.2%), weight loss (10.5 %)], hypertension, etc. have not been adequately addressed for the age group(s) studied.

A review of select cases of Adderall and Adderall XR use from post-marketing AERS showed that prolonged use (e.g. 40 mths) and physical exertion were possibly associated with sudden death in young patients. Strokes, ischemic bowel disease and vasomotor instability seemed to occur much more frequently in females than males. The significance and implication of these observations need to be further explored, analyzed, and discussed within FDA and with an external advisory panel.

VIII. Dosing, Regimen, and Administration Issues

Sponsor's package insert states:

(b) (4)

Patients Currently Using ADDERALL®- Based on bioequivalence data, patients taking divided **doses of immediate-release ADDERALL®, for example twice a day, may be switched to ADDERALL XR® at the same total daily dose taken once daily. Titrate at weekly intervals to appropriate efficacy and tolerability as indicated.**

ADDERALL XR® should be given upon awakening. Afternoon doses should be avoided because of the potential for insomnia."

It is unclear how appropriate efficacy and tolerability will be determined. It is unclear how to mitigate the adverse events, and, or prevent more serious adverse events from occurring.

IX. Use in Special Populations

A. Evaluation of Sponsor's Gender Effects Analyses and Adequacy of Investigation

The gender effect analyses appears to be adequate. The presence of a higher incidence of headaches, palpitations and anorexia in females during these studies and the higher amount of strokes and vasomotor instability in select cases of post-marketing AER's sampled, suggests further studies in females are needed.

B. Evaluation of Evidence for Age, Race, or Ethnicity Effects on Safety or Efficacy

The *age* range examined in Study 303 and 304 were 18-76 years (mean: 39.2 yrs). Elder subjects were under-represented in this sample[71] Older subjects (≥ 40 years) were more likely to report AE's than younger subjects. Young subjects (≤ 40 years) appeared more likely to experience anorexia and weight loss than older subjects. Elderly subjects with renal, hepatic or cardiovascular impairment were not studied. The Change in ADHD-RS Total from baseline to endpoint (LOCF) were reasonably similar in the subjects ≤ 40 years and ≥ 40 years of age.

Women showed a higher incidence of headaches (29.5%, men; 37.4%, women), palpitations (2.7% men; 9.1% women), and anorexia (35.6% men; 45.5% women). *Men* showed a higher of nervousness (25.5% men; 18.2% women). A preliminary review of post-marketing AER's showed that females were more likely then men to develop strokes and show vasomotor instability. In study 303, more males than females were present in the placebo, 20 mg and 40 mg groups (1.4-2:1) than in the 60 mg group, which had more females. Further studies in larger female populations are probably needed. The Change in ADHD-RS Total from baseline to endpoint (LOCF) by treatment group for males and females were not significantly different.

Non-Caucasian was more likely to experience anorexia, nausea, and tachycardia and less likely to experience constipation and weight loss than *Caucasians*. Limited conclusions can be made since there were only 27 non-caucasians in the sample. Further studies with greater racial diversity are probably needed. A significant treatment effect (ADHD-RS) was seen in the non-Caucasians and Caucasians.

71 Age ranges were grouped by a range of 9-11 years, except for those over 50 years who had a range of 26 years.

C. Evaluation of Pediatric Program

The original NDA was approved based on the demonstration of acceptable safety and efficacy in a 3 week treatment trial (Study 301). ADHD is a chronic disorder requiring children to remain on the drug for many years. The referenced post-marketing AER's adverse events and referenced literature indicates that serious, if not fatal adverse events may possibly be associated with chronic use and, or, physical exertion. Hence, long-term safety data is critically needed.

Changes in blood pressure and heart rate were shown in the NDA (e.g. study 201, mean sitting SBP of +7 mmHg vs. –1 mmHg for placebo) and in published studies, however, no limited information is available on the long-term effect of these changes. Stow[72] ET. AL. performed 24-hour ambulatory blood pressure monitoring (ABPM) in 9 male children (7-11 years of age, avg: 8.9 years) receiving chronic Adderall therapy at a dose of 0.5 ± 0.3 mg/kg for 6.1 ± 3.9 months, both off and on drug, showing significant differences between awake and sleep hours. DBP load calculated from ABPM reference data was increased significantly (9.0% +/- 5.6% on and 4.8% +/- 4.5% off therapy; $p < 0.05$) while subjects were taking Adderall. There was a trend toward a greater elevation in blood pressure load during awake hours and a more pronounced decrease during the asleep hours for periods on compared with off-stimulant therapy. This trend resulted in significant ($p < 0.05$) nocturnal dipping on-stimulant phases compared with off-stimulant therapy for both SBP and DBP (Adderall). Static blood pressure monitoring may be insufficient to characterize the real cardiovascular changes which are occurring on a day to day basis.

Treatment emergent ECG abnormalities of various types were reported which were considered clinically insignificant, but, this should be revisited in the context of the post-marketing AER's.

D. Comments on Data Available or Needed in Other Populations

Data is critically needed on long-term use, so as to define the optimum duration of treatment, and, or identify subjects (patients) who will be at risk for developing a serious adverse event. Given that Adderall XR was associated with a high amount

72 Stowe CD, Gardner SF, Gist CC, Schulz EG, Wells TG. 24-hour ambulatory blood pressure monitoring in male children receiving stimulant therapy. Ann Pharmacother. 2002 Jul-Aug; 36(7-8):1142-9.

of anxiety and depression, further drug-drug interaction studies are needed for the commonly used SSRI's and anxiolytics. Further information is needed to assess cardiovascular, cerebrovascular and peripheral vascular risks associated with the use of Adderall XR. Refer to comments on gender, age and ethnicity.

X. Conclusions and Recommendations

A. Conclusions

In Study 303, treatment with Adderall XR was statistically superior to placebo on the primary efficacy measure, ADHD-RS total score, in the 20, 40, and 60 mg groups. However, the clinical meaning of statistical significance on the ADHD-RS is uncertain because of: 1) lack of demonstrated validity in the ADHD-RS in the adult population; 2) the scale does not appear to have been modified for adults; and 3) no inter-rater, inter center and subject and center reliability studies are apparent. In addition, in this reviewer's opinion, there is diagnostic uncertainty that all the subjects had ADHD, or, that the symptoms could have been explained by co-morbid neuro-psychiatric disorders.

Many serious safety issues were identified which need to be better characterized prior to recommending approval.

B. Recommendations

Issue(s) Relating to Diagnosis of ADHD and Efficacy:

1. The primary efficacy, ADHD-RS, as developed by DePaul was apparently "revised for adults by Spencer et al. (1995) and Wilens et.al. (1996,1998)". Identify what specific modifications for adults were made from the original instrument used by DePaul to Spencer, Wilens et. Al. to the final instrument used by you, during your clinical trial. Provide normative data for the adult version of the scale used during the clinical trial and demonstrate that the instrument has satisfactory sensitivity and reliability in the intended population. Demonstrate the appropriateness of this measurement (9.1.4; pg. 32 of the 301 Clinical Study Report) and that ".. are standard measurements currently employed in adult ADHD studies. It has norms derived from sample populations, and demonstrates good reliability and validity." Please explain how items 1 (Difficulty Remaining Seated), 3 (Difficulty Playing Quietly), 4 (Talk Excessively) and 9 (Blurts Out Answers) are specific to adult ADHD?

2. In study 303 and 304, the ADHD-RS was completed by subjects with a clinician with reference to their ADHD symptoms

during the prior week. Please explain how reliability was achieved? What were the inter-rater reliabilities between subject and rater, between raters, and between centers? How many different raters were used for each subject?

3. Provide the results and an analysis of the SCID-1 psychiatric interview excluding co-morbid disorders; and the KBIT (IQ Scale) at screening. These were not submitted with this NDA making it difficult to further characterize this population.

4. The literature that you provided indicates that the diagnosis of adult ADHD is dependent upon a childhood history of ADHD (to confirm that the symptoms were present *before 7 years*), a history of school problems[12], family history[12], a complete psychiatric evaluation to *exclude other or co-morbid* psychiatric *disorders*, possible neuropsychological testing to evaluate possible sequelae of TBI or a degenerative process, and a careful medical history, etc.[2] In the April 14, 2002 meeting we agreed that for diagnostic purposes, a patient's verbal statement about the onset of his or her ADHD symptoms beginning prior to 7 years of age would be accepted. This was presumably ascertained by asking the subject if item B of the DSM-IV TR was correct (B. Some hyperactive-impulsive or inattentive symptoms that caused impairment were present before the age of 7 years). In this study, the average length of time since ADHD diagnosis was 5.4 (± 8.30) years. In reviewing CRF's of many subjects with adverse event drop-outs, some subjects[73] were diagnosed with ADHD on the day of entry into the study. This is further complicated by the fact that substance abuse and malingering[74] may be common in adult ADHD. Some subjects may also have had co-morbid conditions that could have explained the ADHD symptoms. Other causes of attention difficulties were present in several subjects in which CRF's were audited[75]. Please clarify and please provide us with the above

73 Subjects 103-111 was screened and diagnosed with ADHD on 03/13/02. Subject 104-003 was screened and diagnosed with ADHD on 02/20/02. Subject 104-011 was screened and diagnosed with ADHD on 02/27/02. Subject 129-037 was diagnosed on 03/25/02 and screened on 03/25/02; Subject 113-011 was diagnosed on 02/02/02 and screened on 03/25/02; etc.

74 Quinn CA. Detection of malingering in assessment of adult ADHD. Archives of Clinical Neuropsychology 18 (2003) 379–395.

75 Head trauma-concussion (subject 124-009), head trauma from a MVA (Subject 115-012, head trauma with resulting coma (Subject 124-001).

information to ensure us that each subject in study 303 and 304 had adult ADHD, and nothing else.

5. Subjects had to discontinue all medications at least 7 days prior to randomization at Visit 2. How was this confirmed?

Issues Relating to Safety:

1. Select AE's identified in the ISS and a review of select post-marketing AERS cases indicates that it may be dangerous to give Adderall XR, both short and long-term to adults who are already at risk for heart disease and stroke. Insufficient information is currently available to fully quantify that risk for the purposes of appropriate labeling for use in adults. Longer term exposure and further assessment of cardiac function are clearly indicated. The exact nature of these studies need further discussion and advisory input. A cardio-renal consult on the effects of chronic blood pressure and heart rate increases in adults should be obtained.

2. The interim analysis of Study 304 coupled with the post-marketing AER's suggests that the exposure duration is inadequate. Consideration should be made to wait for the completion of Study 304 at 24 months, and, or, possibly extending it beyond that to 36 months. In the interim, a BLACK BOX WARNING is recommended based upon the present available information:

> "During the marketing of Adderall IR and XR, serious and, or fatal, adverse events have been reported. These adverse events have included stroke, myocardial infarction, cardiac arrhythmia and sudden death in both adults and children. The prescribing physician should consider health risks versus expected benefits."

Warning labels, such as this, may not be able to prevent sudden adverse events occurring with chronic, normal stimulant use, especially when precipitated by physical exertion. An advisory panel is recommended to discuss this and other related issue(s) further (e.g. safety of stimulants with long term use).

3. Discuss the impact of many of these adverse events [e.g. increased depression and anxiety; anorexia (33%), insomnia (27.2 %), headache (26.2%), weight loss (10.5 %)] on the 18-76 age group studied. Do subjects who are chronically

treated with Adderall XR adapt to these adverse events? If not what is the expected impact on their health? For example, increased DBP may be associated with increased risk of stroke and coronary heart disease; or, insomnia may be a major risk factor for depression in the elderly (≥60 years)[76]. Worsening anxiety and depression in this population, as indicated from study 303 to 304, necessitates drug interaction studies (e.g. SSRI's, anxiolytics, etc).

4. In the ISS, you defined vital signs as being abnormal based upon being outside of the following ranges[77]: Pulse (50-100 bpm), Respiration (10-20 bpm), Systolic BP (90-160 mm HG) and Diastolic BP (50-90 mm Hg). However, new guidelines issued by the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC7)[78, 79] has defined hypertension and related it to cardiovascular disease risk. In order to help us, define the potential safety risks associated with the use of Adderall XR in adults; you should re-classify all the blood pressures of all subjects from Studies 303 and 304 according to the following normative criteria.

CLASSIFICATION OF BLOOD PRESSURE (BP)*

CATEGORY	SBP MM HG		DBP MM HG
Normal	<120	and	<80
Prehypertension	120–139	or	80–89
Hypertension, Stage 1	140–159	or	90–99
Hypertension, Stage 2	≥160	or	≥100

* See Blood Pressure Measurement Techniques (reverse side)
Key: SBP = systolic blood pressure DBP = diastolic blood pressure

In addition, to the above request, you should use the following data from the Study 303 and 304 (individually and pooled): age, gender, race, weight, height, vital signs of

76 Sukying C, Bhokakul V, Udomsubpayakul U. An epidemiological study on insomnia in an elderly Thai population. J Med Assoc Thai. 2003 Apr;86(4):316-24.

77 Listing 12.2 Out-of-Normal Range Vital Signs, pgs. 5798-5805

78 Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr, Jones DW, Materson BJ, Oparil S, Wright JT Jr, Roccella EJ; National Heart, Lung, and Blood Institute Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; National High Blood Pressure Education Program Coordinating Committee. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. JAMA. 2003 May 21; 289(19):2560-72. Epub 2003 May 14. Erratum in: JAMA. 2003 Jul 9;290(2):197.

79 The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7); http://www.nhlbi.nih.gov/guidelines/hypertension/

all visits, lipid profiles with normative ranges, fasting blood sugars, presence of albuminuria, cigarette smoking and ECG's, to help model the current and future risk for cardiovascular disease for the population that you have studied, and define the impact on cardiovascular and strokes resulting from the use of Adderall XR, both short term (as shown by these studies) and potential long-term over the next 5 years. A careful review of the medical literature should be undertaken so as to help define potential risks associated with chronic Adderall XR therapy in the adult population. Provide the agency with an electronic data set of the same data for each of the subjects who were enrolled in the studies.

5. Distinguish between subjects coded as having anxiety and nervousness in study 303 and 304, and explain why they were coded as separate events [e.g. nervousness (20.6 %), anxiety (9.4 %)]. How are they different? Provide a list of all the reporter codes for anxiety and nervousness. Please recalculate as a single adverse event (e.g. anxiety-nervousness). Please re-code the original NDA, accordingly.

6. Distinguish between subjects coded as being depressed (6.7 %) and those coded as having asthenia (8.1 %)? How was the diagnosis made in each case and how were they different? Provide a list of all the reporter codes for asthenia, and a summary and discussion of all subjects who became depressed and, or, who developed asthenia. Why should they not be considered as a single adverse event?

7. Of all the subjects who had adverse events, which adverse events were new and which adapted to prolonged treatment?

8. In Study 304, mean ADHD-RS at the endpoint examined was statistically significant as a group, but not in the group rolled over from drug with an interruption (p=0.137). Why was this? Provide an analysis of adverse effects following withdrawal of therapy from the available data. A phase IV commitment may need to assess this further.

9. Provide an in depth review of all post-marketing adverse event reporting for amphetamine, Adderall and Adderall XR which relate to death (sudden, or, otherwise), cardiac events (arrhythmias, cardiomyopathy, myocardial infarctions, ET. Al.), stroke, vital sign abnormalities, seizure, infarcted organs and vasomotor instability (e.g.

changes in colors in extremities, or, other parts of the body) providing us with a vignette of each case; a tabular summary listing the event, age, sex, estimated duration of stimulant use, risk factors (e.g. diabetes, hypertension, migraines, prior injuries, etc.), associated exercise with the primary event, other medications, results of autopsy and other pathology reports. This should not be limited to adults, but should include separate and combined reviews for pediatric and adolescent patients. Risks across age groups should be compared. All relevant published literature should also be reviewed, summarized and included, and related to the observed adverse events. If information is missing, please verify that reasonable efforts (due-diligence) has been made to obtain this information.

10. Listing 12.2 of the safety update indicates abnormal vital signs. Examine whether there is a dose response for those with abnormal vital signs.

11. More treatment emergent ECG abnormalities were present in subjects treated with Adderall XR in the original NDA and this, the sNDA. Given our post-marketing observations of AE's relating to sudden death, arrhythmia and myocardial infarction, electronic copies of all ECG tracings from both the original and sNDA should be provided for an independent cardiology review. This should be put in the context of each subject's clinical history and vital signs.

12. Provide a copy of the hospital discharge summary for all subjects who were hospitalized in Study 304.

13. Identify where the following referenced studies 102, 103 and 105 are included in the Safety Data Base (Integrated Summary of Safety)? If there were not included, please provide us with an explanation.
The studies were:
    - Study 102, the single dose bioavailability study in 20 adults;
    - Study 103, the single dose bioavailability study in 21 adults;
    - And, Study 105, the multiple dose pharmacokinetics study in 20 adults.

14. The present data has deficiencies and inaccuracies which need to be corrected prior to relying on it for accurate labeling.

15. Review of the vignettes of subjects who terminated from studies 303 and 304 for adverse events indicates that many more adverse events occurred with each subject. Please clarify how it was determined which adverse event was primary, and please re-calculate with all the adverse events for each subject.

16. Review of many CRF's for these subjects indicates that subjects had adverse events which were not indicated in the vignettes. Past medical history, vital signs, laboratory testing and changes in symptoms, vital signs, laboratory testing were also lacking in many vignettes, preventing the determination of the significance of many of these adverse event(s). Please provide a clearer statement with the above information for each and every subject who left any of the studies because of an adverse event.

17. In reviewing the exposure to drug in the pivotal trial (303), listed in Table 20, and discussed on pg. 79 of Clinical Study Report 381.303, many subjects were exposed for durations longer than the 4 week randomized portion of the trial, where the 20 mg group should have 4 weeks of drug exposure, the 40 mg should have 3 weeks, and the 60 mg should have two weeks. Please explain and reconcile this discrepancy.

Failure(s) in Meeting Pre-NDA Commitment (s)

1. In the pre-NDA meeting the Sponsor estimated that there would be 200 subjects exposed for 6 months in the safety study (381.304). The 4 month safety update (Appendix: Sponsor's Table 4, Extend of Exposure in Multiple Dose Studies) indicates that only 74 (29.8 %) of the subjects were exposed for greater than or equal to 6 months, well below the agreed upon exposure.

2. (b) (4)

(b) (4)

3. (b) (4)

4. We stated that the post marketing data from the narcolepsy patient population may be relevant. However, no post marketing data from the narcolepsy patient population was provided.

5. At our meeting, we raised questions about the possibility of abuse potential in the adult population. Based on the literature, which you submitted[80], greater co-morbidities are present in adults with ADHD, hence, the risk of abuse and the possibility of tolerance or drug refractoriness may be greater in this population. The common comorbidity of substance abuse in adult patients with ADHD may be more of a concern than when a medication is administered by parents. This submission did not deal with these issues. What potential risks and or adverse events resulting from non-compliance would be expected with routine use, and what program could be put into place to deal with this issue?

(b) (4)

80 Findling RL, Dogin JW. Psychopharmacology of ADHD: children and adolescents. J Clin Psychiatry. 1998; 59 Suppl 7:42-9.

81 Submission No. 059

(b) (4)

Other:

1. Provide FDA Forms 3454 for Dr. Biederman and any other consultants whose opinion was relied on and referenced for the adult ADHD program.

2. It is not apparent that post-marketing adverse events were reported for the first three (3) years following drug approval. This should be made current.

3. DSI should re-examine various cases identified within this review(e.g. 115-012).

XI. Appendix

A. Subjects With Serious Adverse Events (304)

These vignettes were provided by the Sponsor with this submission and were included in this review. The areas marked in yellow reflect the different adverse events identified by the reviewer for each of the subjects. A * next to the subject ID denotes that the subjects respective, CRF's were audited.

Adderall XR 20 mg (n=3)

Subject 102-021: Vignette included in Section VII, C (Integrated Review of Safety/Methods and Specific Findings of Safety Review)

Subject 115-012: Vignette included in Section VII, C (Integrated Review of Safety/Methods and Specific Findings of Safety Review)

Subject 112-019, a 60 year-old Hispanic female, started open-label study medication on April 26, 2002 receiving Adderall XR 20 mg. She experienced nephrolithiasis that required hospitalization on (b) (6) when she presented to the hospital with severe left flank pain and left lower quadrant pain consistent with left ureteral obstruction. Recent x-ray (date unknown) had revealed a stone in the distal ureter. She was admitted for IV hydration, pain control and she was started on IV antibiotics. A spiral CT revealed a possible stone in the left ureter with mild hydronephrosis. On (b) (6) she underwent cystoscopy, left ureteroscopy with stone and mucous plug removal, and a left ureteral stent placement. She was discharged home (b) (6) on hydrocodone/ acetaminophen for pain and levofloxacin for prevention of infection. The event was considered resolved with no sequelae and study medication was stopped temporarily for two days during the hospitalization. The investigator determined that the event was not related to the study medication and due to unknown etiology (idiopathic). The patient was withdrawn due to non-compliance on November 22, 2002.

Adderall XR 40 mg (n=1)

Subject 104-038, a 22 year-old Caucasian male started on open-label Adderall XR 20 mg QD on May 3, 2002. His dose of Adderall XR was up-titrated to 40 mg QD on May 10, 2002. On

December 16, 2002 the investigator was informed by the patient's mother that the patient experienced and accidental injury (burn) and was admitted to the hospital on (b) (6). He was holding fuel in his hand while doing car repairs the automobile backfired from the carburetor which resulted in burns to his hand(s). The degree and body percentage of the burns are presently unknown, the patient's mother informed the site that she was told by the treating physician that the patient would be in the hospital for at least (b) (6) In early January, 2003 the site was told by the patient's mother that all communication would be handled through the subject's lawyer, details on this event have been requested by the site. The action taken with the study medication and the patient's status in the trial are unknown at this time. The investigator determined that the event was not related to the study medication and was due to accidental injury.

Adderall XR 60 mg (n=2)

Subject 102-015, a 40 year old Caucasian female, received open-label Adderall XR for ADHD, at 20 mg OD beginning May 8, 2002, and was successfully up-titrated to a maintenance dose of 60 mg by June 5, 2002. She developed a severe headache that required hospitalization and treatment from (b) (6) The SAE was initially reported as a 'headache'. Upon following up with the patient, she reported that she was discharged from the hospital on (b) (6) (b) (6) with a diagnosis of 'bacterial meningitis'. The discharge summary for this hospitalization later clarified a final diagnosis of 'pneumoencephalocele.'

On July 3, 2002, she developed a headache that by (b) (6) (b) (6) had exacerbated and was accompanied by nausea and vomiting. She presented to hospital on (b) (6), was admitted and diagnosed with bacterial meningitis. The subject was treated with IV antibiotic therapy (ceftriaxone), and was discharged home on (b) (6) This event was considered resolved with no sequelae, and discharge medications included ceftriaxone IV and acetaminophen/oxycodone. The subject discontinued the study drug on her own on July 3, 2002.

On July 16, 2002 the subject stated that she was informed that her meningitis was caused by a "dripping of spinal fluid" due to a previous injury to the "membrane covering the meninges" during sinus surgery in 1997. She also stated

that the plan was for her to undergo, at a later date, "cranial facial reflooring" surgery to repair that injury.

On August 21, 2002 the subject related that a cysternogram was done and showed that the meningitis had caused formation of scar tissue in the areas of the brain where cerebral spinal fluid had been leaking. Therefore, the condition resolved and would not require any additional treatment.

Past medical/surgical history included asthma, chronic sinusitis, degenerative spinal disc disease, post-traumatic stress disorder, tubal ligation, functional endoscopic sinus surgery and environmental allergies.

Concurrent medications include loratadine, albuterol, amoxicillin/clavulanic acid, celecoxib, cromolyn, ibuprofen, miconazole, and norelgestromin/ethinyl estradiol, flagyl, unasyn, tylox, dilaudid, phenergan, prinivil, rochepin, and roxicet.

The study drug was permanently discontinued on July 3, 2002, and the subject was withdrawn from the study. The Primary Investigator determined that this event was not related to the study drug but was due to a sinus condition.

Subject 108-005, was a 44 year-old Caucasian female who received double-blind 40 mg Adderall XR from April 3, to May 1, 2002. She entered into the open-label phase of the trial on May 1, 2002 commencing at 20 mg as per protocol from May 2, 2002, and was successfully titrated to 60 mg by May 16, 2002.

The subject was seen by her family physician on June 5, 2002 following a two-week history of abdominal pain, reported as an adverse event leading up to the SAE, and was initially treated with Nexium. The abdominal pain exacerbated and radiated to both sides of the abdomen and to her back. Concurrently she was experiencing nausea, vomiting, and loose stools, for which she presented to the emergency department on June 6, 2002. On examination, the abdomen was soft, with tenderness experienced in the midline and in the right upper quadrant upon palpation, the bowel sounds were audible, and a guiac exam was negative. Initial treatment included intravenous fluids and antibiotics. An abdominal ultrasound performed on (b) (6)

revealed cholelithiasis with mild gallbladder wall thickening, minimal pericholecystic fluid and a positive sonographic Murphy's sign that was indicative of acute cholecystitis. On [redacted] (b) (6) the start date of the SAE, the patient was hospitalized and underwent emergency laparoscopic cholecystectomy that same day. The intraoperative findings were significant for a markedly distended gallbladder, and no overt visual pathology was noted. The gallbladder was surgically excised and removed without difficulty. The early postoperative recovery was uneventful and she was discharged home in stable condition on [redacted] (b) (6) on oxycodone (PRN) for postoperative analgesia. The pathology report subsequently revealed chronic cholecystitis and cholelithiasis with no evidence of malignancy. The study medication was temporarily withheld from June 02-18 due to the cholecystitis.

Past medical history included endometriosis, fibromyalgia and seasonal rhinitis, laparoscopy in 1983 and a right breast lumpectomy in 1999.

Concurrent medications included acetaminophen, acetaminophen/diphenhydramine, acetylsalicylic acid, midazolam, propofol, vercuronium, lactated ringers, oxycodone, ketorolac, fentanyl, Unasyn, docusate sodium, ranitidine, glycopyrrolate, neostigmine, ondansetron. She resumed Adderall 60 mg daily on 19 June 2002, and maintained that dose, as confirmed in follow-up study visits.

The subject remained in the trial and the Primary Investigator determined this event was not related to the study medication, however attributed it to be most likely related to a preexisting medical condition. The action taken for this event was reported as pharmacological by the investigator since the patient received antibiotics and pain medications, and the options given were pharmacological or non-pharmacological.

B. Subjects Who Discontinued Because of An Adverse Event (Study 303)

These vignettes were provided by the Sponsor with this submission and were included in this review. The areas marked in yellow reflect the different adverse events identified by the reviewer for each of the subjects. A * next to the subject ID denotes that the subjects respective, CRF's were audited.

Placebo Group (N=1)

Subject 129-030 was a 44 year-old White male who was ADHD treatment naïve. He started on placebo on 28 March 2002. On 29 March 2002 he experienced moderate agitation and moderate nervousness, both of which were considered to be related to study medication. No treatment was given. He discontinued study medication on 4 April 2002. The adverse events were reported as resolved on 6 April 2002. He was last seen in the study on 4 April 2002.

ADDERALL XR 20 mg (N=9)

Subject 103-104 was a 27-year-old White female with a history of penicillin allergy. She was ADHD treatment naïve. She started ADDERALL XR 20 mg daily on 11 March 2002. On 13 March 2002 she reported severe insomnia, moderate nausea, moderate anorexia, moderate agitation and moderate thirst. All AEs were considered related to study medication. She discontinued study medication on 15 March 2002. The insomnia and nausea were reported resolved on 16 March 2002, and the anorexia, agitation and thirst were reported resolved on 17 March 2002. All resolved without treatment and without sequelae. She was last seen in the study on 18 March 2002. No other adverse events were reported. By the time she discontinued medication, she had been on ADDERALL XR 20 mg for 5 days.

Subject 115-003 was a 38 year-old White male, who was ADHD treatment naïve. He started ADDERALL XR 20 mg daily on 20 March 2002. On 25 March 2002 he reported a moderate craving for cocaine, which was thought to be possibly related to the study medication. No treatment was given. He discontinued study medication on 27 March 2002, and the adverse event resolved on 28 March 2002. He was last seen in the study on 29 March 2002. No other adverse events were reported. By the time he discontinued medication, he had been on ADDERALL XR 20 mg for 8 days.

Subject 115-008* was a 29 year-old White female, who was ADHD treatment naïve. She started on ADDERALL XR 20 mg daily on 29 March 2002. On 30 March 2002 she experienced mild dry mouth, mild nervousness, mild amnesia (forgetfulness) and mild anorexia. The dry mouth, nervousness and anorexia were thought to be related to the study medication, while the amnesia was thought possibly to be related. No treatment was given for these adverse events. She discontinued study medication on 5 April 2002. All the adverse events were unresolved at the time she was last seen in the study, 5 April 2002. By the time she discontinued medication, she had been on ADDERALL XR 20 mg for 8 days.

Subject 117-003 was a 21 year-old White female, who was ADHD treatment naïve. She started on ADDERALL XR 20 mg daily on 6 March 2002. On 20 March 2002 she experienced severe anxiety, which was possibly related to study medication. No treatment was given. She discontinued the study medication on 21 March 2002. On 22 March 2002 she experienced a mild panic attack, which was possibly related to study medication. No treatment was given and the panic attack resolved on the same day. The severe anxiety was reported as resolved on 28 March 2002. She was last seen in the study on 27 March 2002. No other adverse events were reported. By the time she discontinued medication, she had been on ADDERALL XR 20 mg for 16 days.

Subject 124-003* was a 35 year-old White male who was ADHD treatment naïve. He started on ADDERALL XR 20 mg daily on 27 February 2002. On 14 March 2002 he experienced severe irritability, considered to be related to study medication. No treatment was given. He discontinued study medication on 15 March 2002, and the adverse event was reported resolved on 19 March 2002. He was last seen in the study on 19 March 2002. This subject had several additional adverse events. He experienced moderate watery diarrhea and mild vasodilatation starting on 1 March 2002 and possibly related to the study drug. These resolved on 7 March 2002 and 5 March 2002 respectively. Starting on 14 March 2002, he experienced mild hand tremors, severe agitation, moderate speech disorder (stuttering), and moderate worsening of difficulty concentrating that were definitely related to the study drug. All resolved with discontinuation of the study drug. Finally, on 18 March 2002, after drug discontinuation, he experienced a moderate

viral infection, which was unrelated to study medication. He was last seen in the study on 19 March 2002. By the time he discontinued medication, he had been on ADDERALL XR 20mg for 17 days.

Subject 124-011 was a 28 year-old Asian male whose previous ADHD medication was Bupropion 200 mg daily, January 2002 to March 2002. On 20 March 2002 he started on ADDERALL XR 20 mg. At baseline (20 March 2002) his blood pressure was 120/82 mm Hg. Subsequent blood pressures showed an upward trend: *138/92* mm Hg on 27 March 2002, 138/92 mm Hg on 3 April 2002 and 152/104mm Hg on 10 April 2002. The last value was recorded as an adverse event of moderate elevated blood pressure and moderate tachycardia (106 bpm), both considered to be related to study medication. No treatment was given. He discontinued study medication on 10 April 2002, and the adverse events were unresolved when he was last seen on the study on 10 April 2002. He experienced additional related adverse events of moderate insomnia, starting 20 March 2002 and resolving 23 March 2002, followed by mild insomnia, staring 2 April 2002 and ongoing at end of study. He also experienced an unrelated adverse event of ear disorder (tympanic membrane perforation), which started 10 April 2002 and was ongoing. By the time he discontinued medication, he had been on ADDERALL XR 20 mg for 22 days.

Subject 124-019 was a 51 year-old White male who was ADHD treatment naïve. He started on ADDERALL XR 20 mg daily on 3 April 2002. On 9 April 2002, he experienced severe insomnia, considered to be related to study medication. No treatment was given and he discontinued the study medication on 10 April 2002. The insomnia resolved on 11 April 2002. He was last seen in the study on 12 April 2002. He experienced additional possibly related adverse events of mild taste perversion (metallic taste) and mild dry mouth, starting 6 April 2002 and resolving 12 April 2002, and somnolence, starting 4 April 2002 and resolving April 9 2002. He also experienced unrelated adverse events of mild insomnia, starting 7 April 2002 and resolving 8 April 2002, and mild sunburn, starting 7 April 2002 and resolving 12 April 2002. By the time he discontinued medication, he had been on ADDERALL XR 20 mg for 8 days.

Subject 129-020* was a 41 year-old White male who was ADHD treatment naïve. He started on ADDERALL XR 20 mg daily on

22 March 2002. On 23 March 2002 he experienced moderate tachycardia (pulse rate not recorded) and moderate insomnia, both possibly related to study medication. No treatment was given. He discontinued study medication on 25 March 2002 and both adverse events resolved on 26 March 2002. He was last seen in the study on 28 March 2002. No other adverse events were reported. By the time he discontinued medication, he had been on ADDERALL XR 20 mg for 4 days.

Subject 129-037* was a 43 year-old Hispanic male who was ADHD treatment naïve. He started on ADDERALL XR 20 mg daily on 4 April2002. On 12 April 2002 he experienced moderate hyperkinesia and moderate insomnia, which were considered to be related to study medication. No treatment was given. He discontinued study medication on 16 April 2002. The adverse events were unresolved when he was last seen in the study on 18 April 2002. He experienced additional related adverse events of mild nervousness, starting on 5 April 2002 and unresolved, moderate headache starting on 6 April 2002, which resolved the same day, and moderate agitation and dizziness, starting on 12 April 2002, which were addressed by interruption of study dosing. These were unresolved when he was last seen. By the time he discontinued medication, he had been on ADDERALL XR 20mg for 13 days.

ADDERALL XR 40 mg (N=6)

Subject 113-011* was a 48-year-old White male, who was ADHD treatment naïve. He started titrating up to ADDERALL XR 40 mg daily on 9 April 2002. On 10 April 2002 he reported moderate somnolence, possibly related to the study medication. No treatment was given. He discontinued study medication on 10 April 2002, and the adverse event resolved on 12 April 2002. He was last seen in the study on 16 April 2002. He experienced additional possibly related adverse events of moderate insomnia and moderate anorexia, both starting on 10 April 2002 and resolving on 11 April 2002. By the time he discontinued medication, he had been on ADDERALL XR 20 mg for 2 days.

Subject 115-004* was a 34 year-old Asian female, who was ADHD treatment naïve. She started titrating up to ADDERALL XR 40 mg daily on 21 March 2002. On 22 March 2002 she reported moderate headache, possibly related to the study medication, which was treated with ibuprofen, 400 mg QD. On

23 March 2002 she reported moderate asthenia and moderate dysmenorrhea, both thought possibly to be related to the study medication. The dysmenorrhea was treated with ibuprofen, 400 mg QD. On 25 March 2002 she reported moderate anorexia, possibly related to the study medication. No treatment was given. She discontinued study medication on 26 March 2002. The moderate dysmenorrhea resolved on 26 March 2002, and the anorexia on 27 March 2002. The moderate headache and moderate asthenia were both unresolved when she was last seen in the study on 28 March 2002. She experienced additional possibly related adverse events of mild nausea, starting and resolving on 25 March 2002. By the time she discontinued medication, she had been on ADDERALL XR 20 mg for 6 days.

Subject 122-008 was a 57 year-old White female, who was ADHD treatment naïve. At study entry, mild, non-clinically significant elevations were noted in her alkaline phosphatase (164 IU/L), SGPT (46 IU/L) and GGT (108 IU/L). SGOT was within normal limits. She started titrating up to ADDERALL XR 40 mg on 3 April 2002. On 30 April 2002 her laboratory values showed increasing elevations in alkaline phosphatase (191 IU/L), SGPT (130 IU/L), SGOT (60 IU/L), and GGT (126 IU/L). Total bilirubin was within normal limits, and the patient was asymptomatic. All these adverse events were considered mild in intensity and not related to study medication. Due to the rising trend, she was withdrawn from the medication (last dose 30 April 2002). All the adverse events were unresolved when she was last seen in the study on 30 April 2002. Additional related adverse events experienced by this subject included mild insomnia, starting 4 April 2002 and resolving 5 April 2002, mild anorexia, starting 5 April 2002 and unresolved at study end, mild dyspepsia, starting 13 April 2002 and resolving 15 April 2002, and mild dry mouth, starting 17 April 2002 and resolving 27 April 2002. She experienced unrelated adverse events (laboratory abnormalities) of urine nitrite, bacteria in urine and urinary casts, all mild, all staring 30 April 2002 and unresolved when she was last seen. By the time she discontinued medication, she had been on ADDERALL XR 20 mg for 7 days, followed by ADDERALL XR 40 mg for 21 days.

Subject 124-006 was a 44 year-old White male who was ADHD treatment naïve. He started titrating up to ADDERALL XR 40 mg on 4 March 2002. On 5 April 2002 he experienced moderate

insomnia, considered to be related to the study medication. No treatment was given. The moderate insomnia persisted until 24 March 2002, and then the subject experienced increased insomnia (severe), starting on 25 March 2002, again considered to be related to study medication. No treatment was given and the study medication was discontinued on 27 March 2002. The adverse event was unresolved when the subject was last seen in the study on 27 March 2002. He experienced additional related adverse events of moderate irritability, starting 8 March 2002 and resolved 15 March 2002, followed by mild irritability, starting 16 March 2002 and unresolved at the end of study, and mild oliguria (decreased urinary flow), starting 19 March 2002 and unresolved. He also experienced possibly related adverse events of mild agitation, starting 4 March 2002 and resolving 22 March 2002, mild dyspnea, starting 16 March 2002 and resolved 22 March 2002, mild sweating and mild cold hands, starting 20 March 2002 and unresolved. In addition, he experienced an unrelated adverse event, dental pain due to tooth extraction, from 22 March 2002 to 23 March 2002. By the time he discontinued medication, he had been on ADDERALL XR 20 mg for 7 days, followed by ADDERALL XR 40 mg for 17 days.

Subject 124-009* was a 41 year-old Hispanic male, who was ADHD treatment naïve. He started titrating up to ADDERALL XR 40 mg daily on 13 March 2002. On 14 March 2002, he experienced severe insomnia, mild dry mouth and mild asthenia. The insomnia and dry mouth were considered to be related to study medication, while the asthenia was considered possibly related. On 15 March 2002, he experienced mild chest pain, mild headache and mild tooth disorder (teeth clenching). The headache was considered to be related to the study medication and the chest pain and tooth disorder were considered possibly related. No treatment was given for any of these AEs. The headache resolved on 15 March 2002. He discontinued study medication on 16 March 2002, and the chest pain and dry mouth resolved on 17 March 2002, while the asthenia and tooth disorder resolved on 18 March 2002. He was last seen in the study on 20 March 2002, when his ECG and chest examination were normal. No other treatment-emergent adverse events were reported. By the time he discontinued medication, he had been on ADDERALL XR 20 mg for 4 days.

Subject 130-001* was a 49 year-old White female who had

previously received an unspecified investigational drug for ADHD (last dose May 2001). She started titrating up to ADDERALL XR 40 mg on 1 March 2002. On 2 March 2002 she reported moderately decreased appetite, and on 8 March 2002 she reported moderate weight loss. Her weight at screening was 136 lbs (19 February 2002), and her weight at study termination was 130 lbs (8 March 2002). She discontinued study medication on 7 March 2002. The adverse event was ongoing when she was last seen in the study on 8 March 2002. No other adverse events were reported. By the time she discontinued medication, she had been on ADDERALL XR 20 mg for 7 days.

ADDERALL XR 60 mg (N=8)

Subject 103-111* was a 51-year-old White male who was ADHD treatment naïve. He started titrating up to Adderall XR 60 mg daily on 25 March 2002. On 11 April 2002 he reported moderate nervousness, which was considered related to study medication. No treatment was given. He discontinued study medication on 15 April 2002, and the adverse event was unresolved when he was last seen in the study, on 15 April 2002. Additional treatment-related adverse events were moderate hyperkinesia, starting 26 March and resolved 8 April 2002, moderate anorexia, starting 28 March 2002 and unresolved, moderate agitation, starting 26 March and resolving 8 April 2002, and again starting 11 April 2002 and unresolved at study end, and moderate tooth disorder (teeth clenching), starting 28 March 2002 and resolved 8 April 2002. In addition he experienced a possibly related adverse event of mild myalgia, starting 30 March 2002 and resolving 8 April 2002. By the time he discontinued medication, he had been on Adderall XR 20 mg for 7 days, Adderall XR 40 mg for 7 days and Adderall XR 60 mg for 8 days.

Subject 104-003* was a 76-year-old White male who was ADHD treatment naïve. He started titrating up to Adderall XR 60 mg daily on 4 March 2002. On 26 March 2002, he developed severe insomnia, considered related to the study medication. No treatment was given. He discontinued study medication on 26 March 2002. The adverse event was unresolved when the patient was last seen in the study, on 27 March 2002. He experienced an additional possibly related adverse event of dry mouth, starting 12 March 2002 and unresolved at study end. By the time he discontinued medication, he had been on Adderall XR 20 mg for 7 days,

ADDERALL XR 40 mg for 7 days, and Adderall XR 60 mg for 9 days.

Subject 104-011* was a 34-year-old White male who was treatment naïve. He started titrating up to ADDERALL XR 60 mg daily on 12 March 2002. On 20 March 2002 he experienced moderate tachycardia, moderate sweating, and moderate anxiety, all of which were related to study medication. No treatment was given for any of these AEs. He discontinued study medication on 28 March 2002. All adverse events resolved on 30 March 2002. He was last seen in the study on 3 April 2002. Additional adverse events were moderate dry mouth which developed on 13 March 2002 and resolved 30 March 2002, considered possibly related to the study medication. By the time he discontinued medication, he had been on Adderall XR 20 mg for 7 days, Adderall XR 40 mg for 7 days and Adderall XR 60 mg for 3 days.

Subject 106-009* was a 59-year-old White female who was ADHD treatment naïve. She started titrating up to Adderall XR 60 mg daily on 26 March 2002. On 28 March 2002 she experienced mild headache, considered possibly related to the study medication. The dosing was interrupted and she was treated with paracetamol 500 mg orally PRN and the headache resolved on 29 March 2002. She also experienced possibly related adverse events of diarrhea, starting and resolving on 28 March 2002, and indigestion, starting and resolving on 31 March 2002. Additionally, she experienced related adverse events of mild dry mouth and mild nervousness, starting on 27 March 2002 and unresolved at study's end. Her last dose of study medication was on 3 April 2002. On 4 April 2002 she again reported mild headache, considered possibly related to the study medication. The adverse event was reported resolved when she was last seen in the study on 4 April 2002. By the time she discontinued medication, she had been on Adderall XR 20 mg for 7 days and Adderall XR 40 mg for 2 days.

Subject 116-005 was a 29 year-old White female, whose previous ADHD medication was dexamphetamine, 25 mg daily, from November 2001 to February 2002 for ADHD. She started titrating up to Adderall XR60 mg daily on 1 April 2002. On 2 April 2002 she reported moderate depersonalization (described as a foggy, drugged feeling), thought to be related to the study medication, and abnormal thinking (described as an echo in her head), thought to be possibly

related to the study medication. No treatment was given for either adverse event. She discontinued the study medication on 9 April 2002, and both adverse events resolved on 10 April 2002. She was last seen in the study on 15 April 2002. Additional, unrelated adverse events were moderate sinus infection, starting 2 April 2002 and resolved on 12 April 2002, and mild urinary tract infection, starting 15 March 2002 and ongoing at study end. By the time she discontinued medication, she had been on Adderall XR 20 mg for 7 days and Adderall XR 40 mg for 2 days.

Subject 121-004* was a 37 year-old White male, who was ADHD treatment naïve. He started titrating up Adderall XR 60 mg on 1 April 2002. On 2 April 2002 he reported moderate insomnia, and moderate anxiety, which were both considered to be related to the study medication. No treatment was given. The moderate insomnia persisted until 14 April 2002, and then he reported mild insomnia, starting 14 April 2002, which was considered to be related to the study medication. He discontinued study medication on 15 April 2002. Both the moderate anxiety and the mild insomnia were unresolved when he was last seen in the study, on 15 April 2002. He experienced an additional related adverse event of moderate headache, starting 2 April 2002 and resolving 8 April 2002. By the time he discontinued medication, he had been on Adderall XR 20 mg for 7 days and Adderall XR 40 mg for 7 days.

Subject 124-001* was a 44 year-old White male, whose previous ADHD medications were atomoxetine 60 mg BID, October 2000-August 2001 (as part of an open label trial) and methylphenidate 20 mg daily, August 2001-February 2002. He started titrating up to Adderall XR 60 mg daily on 27 February 2002. On 17 March 2002 he experienced moderate agitation, considered to be related to study medication. No treatment was given. The study medication was discontinued on 20 March 2002. The adverse event was unresolved when he was last seen in the study, 20 March 2002. He experienced several additional adverse events. Related adverse events were moderate insomnia, starting 6 March 2002, mild irritability, starting 17 March 2002 and moderate anorexia, starting 17 March 2002. Possibly related adverse events were mildly decreased libido, starting 6 March 2002, mildly increased cough, 6 March 2002, mild speech disorder (word finding difficulty), 6 March 2002, and moderate flushing, 17 March 2002. Unrelated adverse events were mild worsening

of tinnitus, starting 28 February 2002 and mild worsening of rhinitis, starting 2 March 2002. All these additional adverse events were unresolved when he was last seen. By the time he discontinued medication, he had been on A Adderall XR 20 mg for 7 days, on Adderall XR 40 mg for 7 days, and on Adderall XR 60 mg for 8 days.

Subject 130-014 was a 50 year-old White female who was ADHD treatment naïve and her concomitant medication was ibuprofen. She started titrating up to Adderall XR 60 mg on 8 April 2002. From 9 April to 15 April 2002 she experienced mild intermittent insomnia, considered possibly related to the study medication. No treatment was given. On 16 April 2002 she experienced severe insomnia, considered possibly related to the study medication, for which no treatment was given. On 20 April 2002 she discontinued study medication. The adverse event was ongoing when she was last seen in the study on 22 April 2002. Additional possibly related adverse events included moderate anorexia, starting 9 April 2002, and moderate abdominal pain, starting 13 April 2002; both ongoing at when she was last seen. By the time she discontinued medication, she had been on Adderall XR 20 mg for 7 days and Adderall XR 40 mg for 6 days.

C. Subjects Who Discontinued Because of An Adverse Event (Study 304)

These vignettes were provided by the Sponsor with this submission and were included in this review. The areas marked in yellow reflect the different adverse events identified by the reviewer for each of the subjects. A * next to the subject ID denotes that the subjects respective, CRF's were audited.

The Sponsor states that thirty seven (37; 16.6 %)of the subjects discontinued from study 304 because of AEs, several because of multiple AEs. The most frequently reported AEs leading to discontinuation were insomnia (7 subjects), depression (7 subjects), nervousness (5 subjects), headache (4 subjects) and anxiety(4 subjects).

Adderall XR 20 mg (n=20)

Subject 104-015, a 25-year-old female, entered this extension study on March 21, 2002. At baseline, her physical examination and vital signs were unremarkable and her ECG was abnormal but not clinically significant with a marked sinus arrhythmia with first degree block. She received the first dose of study medication, 20 mg daily, on March 22, 2002. On March 22, 2002, she experienced gastroenteritis (mild and possibly related to study treatment) which led to the discontinuation of study drug. On March 22, 2002, she also experienced moderate dizziness, moderate nausea, and moderately decreased appetite (all possibly related to study treatment). She discontinued study drug on March 27, 2002, and withdrew from the study on March 28, 2002. All adverse events were reported resolved on March 30, 2002.

Subject 106-009, a 59-year-old female, entered this extension study on April 4, 2002. At baseline, her physical examination and vital signs were unremarkable and her ECG was abnormal but not clinically significant with a flat T wave. She received the first dose of study medication, 20 mg daily, on April 5, 2002. On April 6, 2002, she experienced headache (mild and possibly related to study treatment), that led to discontinuation of the study drug. She was treated with paracetamol; the adverse event resolved by April 7, 2002. During her treatment she had hypertonia, chills (both mild and possibly related to study treatment), dry mouth and nervousness (both mild and related to study treatment), which all resolved by the time the patient discontinued the study drug on April 8, 2002.

She withdrew from the study on the same day.

Subject 103-111, a 51-year-old male, with a history of agitation, entered this extension study on April 15, 2002. At baseline, his physical examination was unremarkable and his vital signs and ECG were normal. He received the first dose of study medication, 20 mg daily, on April 16, 2002. On April 16, 2002 he reported agitation; nervousness and anorexia (all moderate and related to study medication). The agitation and nervousness resolved on April 24, 2002, while the anorexia was ongoing at study withdrawal. On August 3, 2002 he experienced agitation and anxiety (moderate and possibly related to study medication), both of which resolved on August 12, 2002. On September 25, 2002 he experienced an adverse event of anxiety (severe and not related to study medication), which led to withdrawal from the study and was ongoing at withdrawal. He discontinued study drug (20 mg daily) on September 28, 2002 and withdrew from the study on October 3, 2002.

Subject 113-003, a 46-year-old male, entered this extension study on April 11, 2002. At baseline, his physical examination and vital signs were unremarkable and his ECG was normal. He received the first dose of study medication, 20 mg daily, on April 12, 2002 and was titrated up to 40 mg daily on April 19, 2002. On April 20, 2002, he experienced insomnia (moderate and possibly related to study treatment) which led to down-titration to 20 mg daily on April 26, 2002, and eventual discontinuation of study drug. On April 20, 2002, he also experienced mild dizziness (possibly related to study treatment). On April 26, 2002 he experienced mild amblyopia (possibly related to study treatment). The mild dizziness resolved by July 10, 2002. The insomnia and amblyopia had not resolved by study withdrawal. He discontinued study treatment on July 30, 2002 and withdrew from the study on August 7, 2002.

Subject 115-008, a 29-year-old female, entered this extension study on April 5, 2002. At baseline, her physical examination was unremarkable and her vital signs and ECG were normal. She received the first dose of study medication, 20 mg daily, on April 6, 2002. On April 6, 2002, she experienced dry mouth, nervousness, anorexia (all mild and related to study treatment) and amnesia (mild and possibly related to study drug) which led to the discontinuation of study drug (20 mg daily) on April 11,

2002; the adverse events did not resolve by study discontinu-ation. She withdrew from the study on April 12, 2002.

Subject 116-001, a 57-year-old male, entered this extension study on April 3, 2002. At baseline, his physical examination was unremarkable and his vital signs and ECG were normal. He entered the open-label study having reported moderate flatulence (possibly related to study treatment) which started on March 29, 2002 but resolved by April 4, 2002. He received the first dose of study medication, 20 mg daily, on April 4, 2002. On April 3, 2002, he experienced moderate pain (i.e., body aches) (not related to study treatment). On April 4, 2002, he experienced insomnia (mild, possibly related to study treatment; resolved by April 14, 2002). Further, on April 4, 2002, he experienced hyperkinesia, insomnia, abnormal thinking (all mild and possibly related to study treatment), mild hypertonia (i.e., clenching of fists and clinching of jaw), moderate agitation (both definitely related to study treatment), and moderate flu syndrome (not related to study treatment). On April 5, 2002, he experienced headache (moderate, possibly related to study treatment; treated with naproxen and resolved on same day). On April 9, 2002, he again experienced headache (moderate, possibly related to study treatment; treated with paracetamol and resolved on April 10, 2002). The adverse events of insomnia and headache led to the discontinuation of study drug (20 mg daily). All adverse events resolved by study withdrawal. He discontinued study drug on April 13, 2002, and withdrew from the study on April 18, 2002.

Subject 116-010, a 57-year-old female, entered this extension study on April 30, 2002. At baseline, her physical examination, vital signs and ECG were normal. She received the first dose of study medication, 20 mg daily, on an unknown date. On May 1, 2002, she experienced dry mouth (severe and possibly related to study treatment) which led to the discontinuation of study drug. Also, on May 1, 2002, she experienced agitation, decreased libido, and emotional lability (all severe and possibly related to study treatment), body aches (moderate and possibly related to study treatment), anorexia, hyperkinesia, headache, and constipation (mild and possibly related to study treatment); The adverse event of dry mouth resolved on May 5, 2002, and all other adverse events resolved by May 17,

2002. She discontinued study drug on an unknown date and withdrew from the study on May 2, 2002.

Subject 124-011*, a 28-year-old male, entered this extension study on April 10, 2002. At baseline, his pulse and diastolic blood pressure were high but not clinically significant, his physical exam was unremarkable and his ECG was normal. He received the first dose of study medication, 20 mg daily, on April 11, 2002 and his last dose on July 22, 2002. He discontinued study drug (20 mg daily) on July 22 2002 because of worsening of hypertension (severe and possibly related to study treatment). At the time of this event the subject was still receiving 20 mg daily of ADDERALL XR. During his treatment he had mild continuous insomnia (possibly treatment related) which continued up to study withdrawal. He withdrew from the study on July 22, 2002.

Subject 126-004, a 25-year-old female, entered this extension study on April 3, 2002. At baseline, her physical examination and vital signs were unremarkable and her ECG was normal. She received the first dose of study medication, 20 mg daily, on April 4, 2002 and was titrated up to 40 mg daily on April 11, 2002. On April 4, 2002, she experienced mild dry mouth (related to study treatment) On April 11 2002 she experienced severe weight loss and moderate insomnia (both related to study treatment) which led to the down-titration of study treatment to 20 mg daily on April 16, 2002, and eventual discontinuation of study treatment on April 29, 2002. The AEs did not resolve by study withdrawal. She withdrew from the study on May 13, 2002.

Subject 126-006, a 52-year-old male, entered this extension study on April 9, 2002. At baseline his physical examination revealed a minor right half tremor, his vital signs and ECG were normal. He received the first dose of study medication, 20 mg daily, on April 9, 2002. On April 10, 2002, he experienced anorexia (moderate and possibly related to study treatment) which led to the discontinuation of study drug (20mg daily) On April 10, 2002, he also experienced a urinary tract disorder, somnolence, dizziness, dyspnea and anxiety (all moderate, and possibly related to study treatment). All adverse events were ongoing at study withdrawal. He discontinued study drug on May 9, 2002 and withdrew from the study on

May 21, 2002.

Subject 129-023, a 25-year-old male, entered this extension study on April 30, 2002. At baseline, his physical examination was unremarkable and his vital signs and ECG were normal. He received the first dose of study medication, 20 mg daily, on May 1, 2002. On May 1, 2002, he experienced insomnia (moderate and related to study treatment), moderate increased libido (possibly related to study treatment), moderate genital edema (not related to study treatment), and mild nervousness (possibly related to study treatment), all of which led to the discontinuation of study drug (20 mg daily) on May 7, 2002. He withdrew from the study on May 7, 2002, and all adverse events were reported resolved on May 14, 2002.

Subject 130-001, a 49-year-old female, entered this extension study on March 8, 2002. At baseline, her physical examination and vital signs were unremarkable and her ECG was normal. She received the first dose of study medication, 20 mg daily, on March 9, 2002. On March 9, 2002, she experienced insomnia (moderate and related to study treatment) which led to the discontinuation of study drug (20 mg daily). On March 9, 2002, she also experienced sweating, anorexia, palpitation (all moderate and related to study treatment) and weight loss (moderate and related to study treatment). She discontinued study drug (20 mg daily) on March 12, 2002. The insomnia, sweating, anorexia and palpitation all resolved by March 13, 2002, and the weight loss resolved by March 19, 2002. She withdrew from the study on March 19, 2002.

Subject 130-008, a 21-year-old male, entered this extension study on April 11,2002. At baseline, his physical examination and vital signs were unremarkable and his ECG was normal. He received the first dose of study medication, 20 mg daily, on April 12, 2002. On April 13, 2002, he experienced weight loss (moderate and related to study treatment) which led to the discontinuation of study drug (20 mg daily). On April 13, 2002, he also experienced insomnia and anorexia (both moderate and related to study treatment; both resolved by May 1, 2002). Other adverse events not related to study drug included a respiratory disorder and accidental injury. He discontinued study drug (20 mg daily) on April 29, 2002 and withdrew from the study on the same day. The insomnia and anorexia were reported

both resolved on May 1, 2002, and the weight loss on May 6, 2002.

Subject 104-040, a 48-year old female, entered this extension study on May 7, 2002. At baseline, her physical examination was unremarkable and her vital signs and her EGG showed nonspecific T-wave abnormality with a long QT interval (read as 404 ms). She received her first dose of study medication (20 mg daily) on May 8, 2002. On May 8, 2002 she experienced depression (mild and possibly related to study medication), which resolved on May 14, 2002. On May 22, 2002, a prolonged QT interval was measured (mild and possibly related to study medication), which was resolved on repeat measurement on June 3, 2002. On May 23, 2002, she experienced dry mouth (mild and possibly related to study medication), which resolved on October 9, 2003. On July 8, 2002 she experienced pain (leg aches, mild and not related to study medication), and on July 15, 2002 she experienced flu syndrome (mild and not related to study medication). The flu resolved on July 22, 2002, and the leg aches on September 12, 2002. On August 21, 2002 she experienced nervousness (mild and possibly related to study medication), and on August 28, 2002 she experienced depression (mild, and possibly related to study medication). All adverse events were reported resolved on October 9, 2002. She took the last dose of study medication (20 mg daily) on October 7, 2002 and withdrew from the study on October 21, 2002, on account of the second episode of depression.

Subject 112-024, a 50-year-old female with a history of constipation, entered this extension study on April 23, 2002. At baseline, her physical examination was unremarkable and her vital signs and EGG were normal. She received the first dose of study medication (20 mg daily) on April 24, 2002. On April 23, 2002 she experienced constipation (mild and possibly related to study medication), on April 24, 2002 she experienced increased thirst (moderate and possibly related to study medication, and on April 25, 2002 she experienced headache (severe and possibly related to study medication. The headache resolved April 26, 2002, and the increased thirst on September 2, 2002. Her dose was increased to 40 mg daily on 30 April 30, 2002. On May 14, 2002 she reported dry mouth (moderate and possibly related to study medication), and on May 19, 2002 she experienced low back pain (moderate and not related to

study medication), which resolved on June 10, 2002. On June 10, 2002 she experienced a manic reaction (moderate and possibly related to study medication). Her dose was reduced to 20 mg daily on June 25, 2002, and the manic reaction resolved on June 27, 2002. On September 9, 2002 she experienced insomnia (moderate and possibly related to study medication), which was unresolved by study withdrawal. The adverse events of constipation and dry mouth were also ongoing at study withdrawal. She took the last dose of study medication (20 mg daily) on September 23, 2002, and withdrew from the study on the same day, on account of the insomnia.

Subject 124-003, a 35-year-old male with a history of tension headaches, episodic back pain, and seborrhea, entered this extension study on March 19, 2002. At baseline, his physical examination was unremarkable and his vital signs and ECG were normal. He received his first dose of study medication (20 mg daily) on March 19, 2002. On March 19, 2002 he reported anorexia and weight loss (both mild and possibly related to study medication). The weight loss resolved on August 15, 2002. On March 20, 2002 he reported dry mouth (mild and related to study medication). On March 21, 2002 he reported nervousness (moderate and related to study medication), which resolved on March 26, 2002. On May 9, 2002 he experienced asthenia (moderate and not related to study medication), which resulted in an interruption of dosing, and resolved on May 10, 2002. On May 16, 2002, he experienced insomnia (moderate and possibly related to study medication), which resolved on May 17, 2002. On May 13, 2002, he experienced contact dermatitis (moderate and not related to study medication), which resolved on June 2, 2002. On May 20, 2002 he experienced headache (moderate and possibly related to study medication), which resolved on the same day. On June 1, 2002 he experienced asthenia (mild and not related to study medication), nervousness (mild and possibly related to study medication), and drug dependence (increased alcohol intake, mild and not related to study medication). These AEs resolved on June 14, 2002, September 8, 2002, and June 12, 2002 respectively. On June 7, 2002 he experienced insomnia (mild and possibly related to study medication), which resolved on June 9, 2002. On August 19, 2002 he experienced depression (moderate and not related to study medication), which was unresolved at study withdrawal. On September 8, 2002 he experienced insomnia (moderate and

possibly related to study medication), which resolved on September 9, 2002, and on September 9, 2002 he experienced nervousness (moderate and possibly related to study medication), which resolved on September 14, 2002. He took the last dose of study medication (20 mg daily) on September 14, 2002 and withdrew from the study on September 17, 2002, on account of the depression.

Subject 124-012, a 44-year-old male, entered this extension study on April 22, 2002. At baseline, his physical examination was unremarkable and his vital signs and ECG showed sinus bradycardia (53 bps). He received his first dose of study medication (20 mg daily) on April 23, 2002. On April 23, 2002 he experienced dry mouth (mild and related to study medication). On May 8, 2002 he experienced nervousness (moderate and related to study medication). His dose was reduced from 40 mg to 20 mg, and the nervousness resolved on May 9, 2002. On May 21, 2002, he again experienced nervousness (mild and related to study medication), which was resolved on August 17, 2002. The dry mouth was ongoing. He took the last dose of study medication (20 mg daily) on August 16, 2002 and withdrew from the study on the same day on account of nervousness.

Subject 129-031, a 45-year-old male with a history of chronic lower back pain, entered this extension study on April 24, 2002. At baseline, his physical examination was unremarkable and his vital signs and ECG were normal. He received his first dose of study medication (20 mg daily) on April 25, 2002. On April 25, 2002 he reported dry mouth (mild and possibly related to study medication), and weight loss (mild and related to study medication). The dry mouth resolved on June 4, 2002. On May 2, 2002 he experienced worsening of the weight loss (moderate and related to study medication) which resolved on June 17, 2002. On May 7, 2002 he experienced insomnia (moderate and possibly related to study medication), which resolved the same day. On May 8, 2002 he experienced nervousness (mild and possibly related to study medication), which led to a decrease in dose from 60 mg daily to 40 mg daily, and which resolved on May 24, 2002. On May 8, 2002 he also experienced hypertonia (teeth clenching, mild and possibly related to study medication), which resolved on June 6, 2002. On May 11, 2002 he experienced anorexia (mild and possibly related to study medication), which resolved on June 5, 2002. On May 25, 2002 he experienced nervousness (moderate and related to

study medication), which resolved on June 6, 2002, but recurred on June 18, 2002 (moderate and related to study medication) On June 20, 2002 he reported weight loss (mild and related to study medication). On June 23, 2002 he experienced worsening of lower back pain (moderate and not related to study medication), which resolved on August *14,* 2002. On July 22, 2002 he experienced headache (moderate and not related to study medication), which resolved on the same day. He took the last dose of study medication (20 mg daily) on July 24, 2002. The adverse event of nervousness resolved on July 26, 2002, while the weight loss was ongoing. He withdrew from the study on August 7, 2002, on account of nervousness.

Subject 130-014, a 50-year-old female with a history of intermittent headaches, decreased appetite, insomnia, and drug and environmental allergies, entered this extension study on April 22, 2002. At baseline, her physical examination was unremarkable and her vital signs and ECG were normal. She received her first dose of study medication (20 mg daily) on April 23, 2002. On April 23, 2002 she reported anorexia and insomnia (both moderate and possibly related to study medication), which resolved on May 10, 2002 and May 7, 2002 respectively. On May 14, 2002 she experienced palpitations (moderate and possibly related to study medication) which continued until May 17, 2002 and then were reported as mild (possibly related to study medication), from May 18, 2002 until resolution on June 1, 2002. On May 14, 2002 she also experienced abdominal pain and anorexia (both mild and possibly related to study medication) and insomnia (moderate and possibly related to study medication), all of which resolved on September 17, 2002. On May 27, 2002 she reported dry mouth (moderate and possibly related to study medication) which resolved on 17 September 2002. On 16 July 2002 she reported agitation (moderate and possibly related to study medication), which resolved on August 13, 2002. On August 7, 2002 she experienced contact dermatitis (poison ivy, moderate and not related to study medication), which resolved on August 11, 2002. On August31, 2002 she experienced depression (moderate and possibly related to study medication), which resolved on September is, 2002. She took the last dose of study medication (20 mg daily) on September 18, 2002 and withdrew from the study on September 20, 2002, on account of depression.

Subject 121-004, a 37-year-old male with a history of anxiety, headaches and insomnia, entered this extension study on April 15, 2002. At baseline, his physical examination was unremarkable and his vital signs and ECG were normal. He received his first dose of study medication (20mg daily) on April 17, 2002. On April 17, 2002 he reported anxiety and insomnia (both mild and possibly related to study medication), both of which resolved on the same day. On April 21, 2002 he experienced myalgia (moderate and not related to study medication), which resolved on April 22, 2002. On April 28, 2002 he experienced chest pain (upon respiration, mild and not related to study medication), which resolved on May 17, 2002. On May 1, 2002 he reported dry mouth (moderate and possibly related to study medication). On August 12, 2002 he experienced asthenia (moderate and possibly related to study medication), on August 13, 2002 he experienced nervousness (moderate and possibly related to study medication), and on August 15, 2002 he experienced anxiety (mild and possibly related to study medication) and depression (moderate and not related to study medication). The dry mouth, asthenia, nervousness, anxiety and depression were all unresolved at study withdrawal. He took the last dose of study medication (20 mg daily) on September 3, 2002 and withdrew from the study on September 9, 2002 on account of asthenia, nervousness, depression and anxiety.

Adderall XR 40 mg (n=11)

Subject 112-007, a 40-year-old male, entered this extension study on April 11, 2002. At baseline, his physical examination and vital signs were unremarkable and his ECG was normal. He received the first dose of study medication, 20 mg daily, on April 12, 2002 and was titrated up to 40mg daily on April 19, 2002. On May 30, 2002, he experienced anxiety (moderate and possibly related to study treatment) which led to the discontinuation of study drug. On May 15, 2002, he also experienced moderate nervousness (possibly related to study treatment and resolved by May 24, 2002). He discontinued study drug (40 mg daily) on June 11, 2002; the anxiety resolved by June 12, 2002. He withdrew from the study on June 11, 2002.

Subject 112-023, a 29-year-old male, entered this extension study on April 22, 2002. At baseline, his physical examination was unremarkable, his respiration rate was

abnormally high but not clinically significant, and his ECG was normal. Some baseline laboratory results (ALP, ALT, GGT, cholesterol, LDL, VLDL, and triglycerides) were abnormally high but not clinically significant. He received the first dose of study medication, 20 mg daily, on April 23, 2002 and was titrated up to 40 mg daily on May 1, 2002. On May 20, 2002, his liver function tests were clinically significantly abnormal (mild and possibly related to study treatment) which led to the discontinuation of study drug (40 mg daily) on June 17, 2002; the adverse event did not resolve by study withdrawal on June 20, 2002.

Subject 113-010, a 48-year-old female, entered this extension study on May 8, 2002. At baseline, her vital signs were unremarkable, her physical examination revealed a poorly visualized fundus, and her ECG was normal. She received the first dose of study medication, 20 mg daily, on May 8, 2002 and was titrated up to 40 mg daily on May 21, 2002. On July 12, 2002, she experienced palpitation (moderate and possibly related to study treatment) which led to the discontinuation of study drug: the adverse event resolved by August 5, 2002. On July 15, 2002, she also experienced moderate rash (possibly related to study treatment). The palpitation resolved by August 5, 2002, and the rash had not resolved by study withdrawal. She discontinued study drug (40 mg daily) on August 5, 2002, and withdrew from the study on August 7, 2002.

Subject 117-004, a 49-year-old male, entered this extension study on April 2, 2002. At baseline, his physical examination was unremarkable, his vital signs and ECG were normal and some baseline laboratory results (cholesterol, VLDL and triglycerides) were abnormally high but not clinically significant He received the first dose of study medication, 20 mg daily on April 3, 2002 and was titrated up to 40 mg daily on April 10, 2002. On April 4, 2002, he also experienced hyperlipemia (i e elevated triglycerides) (moderate and not related to study treatment). On April 12, 2002, he experienced anxiety (moderate and related to study treatment). On April 23, 2002, he experienced hypercholesteremia (clinically significant elevated VLDL) (moderate and not related to study treatment; did not resolve by study discontinuation) which led to the discontinuation of study drug. On April 20, 2002, he experienced moderate headache (possibly related to study treatment; treated with naproxen). The headache resolved on

April 20, 2002, the anxiety resolved on April 23, 2002, and the hypercholesterolemia and hyperlipidemia had not resolved by study withdrawal. He discontinued study drug (40 mg daily) on April 22, 2002 and withdrew from the study on April 23, 2002.

Subject 117-011, a 39-year-old male, entered this extension study on April 15, 2002. At baseline, his diastolic blood pressure was high but not clinically significant, his physical examination revealed obesity, but his ECG was normal. He received the first dose of study medication, 20 mg daily, on April 16, 2002, and titrated up to 40 mg daily on April 23, 2002. He discontinued study drug (40 mg daily) on April 29, 2002 because of hypertension (mild and not related to study treatment, which did not resolve by study discontinuation). The patient withdrew from the study on the same day.

Subject 128-005, a 46-year-old male, entered this extension study on April 3, 2002. At baseline, his physical examination and vital signs were unremarkable and his EGG was normal. He received the first dose of study medication, 20 mg daily, on April 4, 2002, and titrated up to 40 mg daily on April 25, 2002. On April 6, 2002, he experienced impaired urination (i.e., delay with urination) (moderate and possibly related to study treatment) and on May 1, 2002 he experienced palpitation and tachycardia (both moderate and possibly related to study treatment) which led to the discontinuation of study drug (40 mg daily) on May 3, 2002; the adverse events resolved by May 5, 2002. He withdrew from the study on May 6, 2002.

Subject 128-006, a 44-year-old female, entered this extension study on April 3, 2002. At baseline, her physical examination and vital signs were unremarkable and her EGG was normal. She received the first dose of study medication, 20 mg daily, on April 4, 2002 and was titrated up to 40 mg daily on April 17, 2002. On April 19, 2002, she experienced depression (mild and not related to study treatment) which led to the discontinuation of study drug (40 mg daily) on April 23, 2002; the adverse event resolved by May 1, 2002. She withdrew from the study on April 24, 2002.

Subject 129-012, an 18-year-old female, entered this extension study on April 11, 2002. At baseline, her

physical examination and vital signs were unremarkable and her ECG was normal. She received the first dose of study medication, 20 mg daily, on April 12, 2002, and titrated up to 40 mg daily on May 9, 2002. On April 12, 2002 she experienced depression (mild and possibly related to study treatment) that worsened to moderate depression by May 5, 2002 (possibly related to study treatment) which led to the discontinuation of study drug. On April 12, 2002, she also experienced moderate anorexia (possibly related to study treatment and resolved by June 7, 2002). Further, on May 31, 2002, she experienced severe dizziness (possible related to study treatment) and severe nausea (related to study treatment), both of which resolved by May 31, 2002. The moderate depression did not resolve by study withdrawal. She discontinued study drug (40 mg daily) on June 5, 2002, and withdrew from the study on the same day.

Subject 116-007, a 24-year-old female with a history of dry mouth, sore throat, insomnia, decreased appetite, frequent urinary tract infection, migraine, and drug and environmental allergies, entered this extension study on May 1, 2002. At baseline, her physical examination was unremarkable, her vital signs were normal and her ECG was normal with the exception of slight tachycardia. She started study medication (20 mg daily) on May 2, 2002. On May 2, 2002 she reported dry mouth (mild and possibly related to study medication), insomnia (mild and possibly related to study medication), anorexia (mild and possibly related to study medication), and pharyngitis (mild and not related to study medication). The anorexia resolved on May 3, 2002, the insomnia on May 4, 2002, and the pharyngitis on May 10, 2002. On May 3, 2002 she experienced bronchitis (moderate and not related to study medication), and on May 4, 2002 she experienced pneumonia (moderate and not related to study medication). The pneumonia resolved on May 8, 2002 and the bronchitis on May 28, 2002. On May 6, 2002, she experienced dry mouth (moderate and possibly related to study medication), which resolved on September *17,* 2002. On May 8, 2002 she experienced nausea (mild and not related to study medication) and vomiting (moderate and not related to study medication), which led to dosing being interrupted until they resolved on May 10, 2002. On the same day she also experienced tachycardia (moderate and possibly related to study medication). On May 12, 2002 she experience diarrhea (mild and not related to study medication), which resolved on May 15, 2002. On May 15, 2002 she reported

weight loss (severe and possibly related to study medication). On May 18, 2002 she reported insomnia (moderate and possibly related to study medication), which resolved on August 28, 2002. On June 17, 2002 she experienced an infection (head cold), which resolved on June 23, 2002. On July 6, 2002 she reported headache (mild and not related to study medication). On July 28, 2002, she experienced hyperkinesia, asthenia and abnormal thinking (decreased concentration; all mild and possibly related to study medication. On 31 July, 2002, she experienced otitis media (moderate and not related to study medication), which resolved on August 21, 2002. The asthenia resolved on August 26, 2002, and the hyperkinesia and abnormal thinking on September 2, 2002. The tachycardia and weight loss remained unresolved at study withdrawal. She took the last dose of study medication (40 mg daily) on October 2, 2002 and withdrew from the study on October 16, 2002, on account of severe weight loss (weight at withdrawal 104 lbs; starting weight in Protocol 381.304, 120 lbs).

Subject 124-006, a 44-year-old male with a history of decreased urinary flow and irritation, entered this extension study on March 27, 2002. At baseline, his physical examination was unremarkable and his vital signs and ECG were normal. He received his first dose of study medication (20 mg daily), on March 28, 2002. On March 28, 2002, he experienced oliguria (mild and related to study medication), and insomnia (mild and not related to study medication). The oliguria resolved on April 2, 2002 and the insomnia on September 30, 2002. On May 28, 2002 he reported nervousness (mild and possibly related to study medication). On October 1, 2002, he experienced insomnia (moderate and possibly related to study medication). The nervousness and insomnia were unresolved by study withdrawal. He took the last dose of study medication (40 mg daily) on October 28, 2002 and withdrew from the study on the same day on account of the insomnia.

Subject 128-009, a 35-year-old female, entered this extension study on April 24, 2002. At baseline, her physical examination was unremarkable and her vital signs and ECG showed flat T-waves. She received her first dose of study medication (20 mg daily) on April 25, 2002. On May 26, 2002 she reported neck pain (due to a tick bite, moderate and not related to study medication). On June 26, 2002 she experienced an unintended pregnancy (considered of

severe intensity and not related to study medication). She took the last dose of study medication (40 mg daily) on November 19, 2002 and withdrew from the study on the same day. The adverse event was unresolved at the time of study withdrawal.

Adderall XR 60 mg (n=3)

Subject 102-012, a 39-year-old female, entered this extension study on April 19, 2002. At baseline, her physical examination was unremarkable and her vital signs and ECG were normal. She received her first dose of study medication, 20 mg daily, on April 20, 2002. On April 20, 2002 she experienced hypesthesia (bilateral numbness in hands, mild, and possibly related to study medication. On April 25, 2002, she experienced hypertonia (bruxism, mild and possibly related to study medication) and somnolence (mild and possibly related to study medication). The hypertonia resolved without treatment on May 2, 2002. On July 11, 2002, she experienced an adverse event of asthma (mild and considered possibly related). On July 15, 2002, she experienced adverse events of agitation (moderate and possibly related), dyspnea (moderate and possibly related), and pain (radiating to left arm, moderate and possibly related). All adverse events were reported resolved by study exit. She took the last dose of study medication (60 mg daily) on August 12 and withdrew from the study on August 13, 2002, discontinuing on account of the agitation, dyspnea, pain, and asthma.

Subject 113-005, a 51-year-old female with a history of elevated CK levels, fibromyalgia, "3 osteoarthritis, gastroesophageal reflux disease, and urinary frequency with low back and suprapubic pain, entered this extension study on April 18, 2002. She started study medication (20 mg daily) on April 19, 2002. On June 6, 2002 she experienced worsening of elevated CK levels (568 U/L, after baseline of 270 U/L). On August 6, 2002 she had measured hypertension (moderate and possibly related). On August 28, 2002, she experienced back pain and pharyngitis (both moderate and not related to study medication). On August 29, 2002 she experienced headache and vasodilitation (both moderate and possibly related to study medication). The headache, vasodilatation and pharyngitis resolved on August 31, 2002. On September 8, 2002 she reported posterior shoulder pain (moderate and not related to study medication), and on October 15, 2002 she reported left knee pain (moderate and

not related to study medication). The elevated CK levels were reported resolved on October 15, 2002. The hypertension, the back pain, the posterior shoulder pain and the left knee pain were unresolved by study end. She took the last dose of study medication (60 mg daily) on September 20, 2002 and withdrew from the study on October 15, 2002 on account of ongoing hypertension (140/100 mmHg).

Subject 128-003, a 40-year-old male, entered this extension study on April 1. 2002. At baseline, his physical examination was unremarkable and his vital signs and ECG were normal. He received his first dose of study medication on April 2, 2002. On August 1, 2002, he experienced new onset depression (moderate and not related to study medication). On August 7, 2002 he reported weight loss (moderate and possibly related to study medication). The weight loss was reported resolved on September 9, 2002, but the depression was ongoing. He took the last dose of study medication (60 mg daily) on July 31, 2002 and withdrew from the study on August 7, 2002 on account of the depression.

D. Tables and Lists

1. List of Investigators

Protocol SLI381.107

S.W. Boellner, M.D., ET. AL., Clinical Study Center, LLC, Little Rock, AR

Protocol SLI381.108

J.C. Kisicki, M.D., ET. AL., MDS Pharma Service, Lincoln, NE

Protocol(s) SLI381.303, SLI381.304

Site No: 102; C.E. Bailey, M.D. ET. AL., Clinical Neuroscience Solutions, Inc., Orlando, FL

Site No: 103; M.D. Banov ET. AL., Northwest Behavioral research Center, Marietta, GA

Site No: 104; L.M. Beckett, M.D., ET. AL., Research Co., Oklahoma City, OK

Site No: 106; S.W. Boellner, M.D., ET. AL., Clinical Study Center, LLC, Little Rock, AR

Site No: 108; A.K. Chrisman, M.D. ET. AL., Duke Child and Family Study Center, Durham, NC

Site No: 121; A.J. Cutler, M.D., ET. AL., Coordinated Research of Florida, Inc., Winter Park, FL

Site No: 122; J.S. Dowben, M.D., ET. AL (303): (b) (4)

Site No: 126; A.G. Feinberg, M.D. ET. AL., Adult Attention Deficit Disorder Center of Maryland, John Hopkins at Green Spring Station, Lutherville, MD

Site No: 128; H. Hassman, D.O., ET. AL., Comprehensive Clinical Research, CNS, P.C., Clementon, N.J.

Site No: 112; D. Kelsh, M.D., ET. AL., Vince and Associates Clinical Research, Overland Park, KS

Site No: 113; A.J. Levine, M.D., ET. AL., Summit Research Network (Colorado), Inc., Denver, CO

Site No: 129; J.L. Miller, M.D., ET. AL., Clinical Neuroscience Solutions, Inc., West Palm Beach, FL

Site No: 115; W.J. Privitera, M.D., ET. AL., FutureSearch Trials, Austin, TX

Site No: 130; R.A. Riesenberg, M.D., ET. AL., Atlanta Center of Medical Research, Atlanta, GA

Site No: 116; Murray H. Rosenthal, D.O., ET. AL., BMR HealthQuest Behavioral and Medical Research, LLC, San Diego, CA

Site No: 117; K.E. Saylor, Ph.D., ET. AL., Neuroscience Inc., Bethesda, MD

Site No: 124; K. Toups, M.D., ET. AL., Bay Area Research Institute, Walnut Creek, CA

Site No: 125; R.H. Weisler, M.D., ET. AL., Raleigh, NC

2. Baseline Characteristics of ITT Population (303)

Table 8: Summary of Subject Demographic and Disease Characteristics for the ITT Population

		Placebo (N=60)	ADDERALL XR™ 20 mg (N=64)	ADDERALL XR™ 40 mg (N=64)	ADDERALL XR™ 60 mg (N=60)	Total (N=248)
Age (Years)	Mean (SD)	39.3 (11.53)	38.8 (11.30)	38.9 (11.23)	39.9 (11.82)	39.2 (11.40)
Gender, n (%)	Male	41 (68.3%)	41 (64.1%)	38 (59.4%)	29 (48.3%)	149 (60.1%)
	Female	19 (31.7%)	23 (35.9%)	26 (40.6%)	31 (51.7%)	99 (39.9%)
Ethnic Origin, n (%)	White	54 (90.0%)	56 (87.5%)	58 (90.6%)	53 (88.3%)	221 (89.1%)
	Black	3 (5.0%)	3 (4.7%)	2 (3.1%)	0 (0.0)	8 (3.2%)
	Hispanic	2 (3.3%)	4 (6.3%)	2 (3.1%)	5 (8.3%)	13 (5.2%)
	Asian/ Pacific Isl.	0 (0.0)	1 (1.6%)	1 (1.6%)	1 (1.7%)	3 (1.2%)
	Native American	0 (0.0)	0 (0.0)	1 (1.6%)	1 (1.7%)	2 (0.8%)
	Other	1 (1.7%)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4%)
Weight (lb)	Mean (SD)	185.9 (42.15)	181.1 (34.29)	185.4 (49.54)	181.6 (36.92)	183.5 (41.03)
Height (in)	Mean (SD)	66.4 (4.42)	67.9 (3.71)	67.7 (3.87)	66.7 (3.71)	67.7 (3.96)
Years since diagnosis	Mean (SD)	5.0 (7.24)	4.6 (6.79)	4.9 (8.57)	7.1 (10.22)	5.4 (8.30)
Most recent prior ADHD Treatment, n (%)	Not listed	43 (71.7%)	45 (70.3%)	43 (67.2%)	44 (73.3%)	175 (70.6%)
	Antidepressants	2 (3.3%)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.8%)
	Bupropion	2 (3.3%)	1 (1.6%)	0 (0.0)	0 (0.0)	3 (1.2%)
	Citalopram	0 (0.0)	0 (0.0)	2 (3.1%)	0 (0.0)	2 (0.8%)
	Dexamphetamine	2 (3.3%)	0 (0.0)	0 (0.0)	2 (3.3%)	4 (1.6%)
	Fluoxetine	1 (1.7%)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4%)
	Methylphenidate	0 (0.0)	1 (1.6%)	1 (1.6%)	0 (0.0)	2 (0.8%)
	Methylphenidate hydrochloride	1 (1.7%)	5 (7.8%)	11 (17.2%)	7 (11.7%)	24 (9.7%)
	Obetrol	5 (8.3%)	9 (14.1%)	5 (7.8%)	6 (10.0%)	25 (10.1%)
	Venlafaxine	1 (1.7%)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4%)
	Other	3 (5.0%)	3 (4.7%)	2 (3.1%)	1 (1.7%)	9 (3.6%)
ADHD-RS Total Score at baseline	Mean (SD)	33.0 (8.75)	31.1 (9.61)	31.3 (8.13)	32.9 (9.83)	NC†
	Median (Min, Max)	31.5 (14, 54)	30.5 (13, 51)	31.0 (13, 49)	34.0 (6, 50)	NC†

† Not calculated

Source: Section 14, Table 1.3.3 and 2.1.1.

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Version Date: 23 September 2002

Prepared by PRA International

3. Schedule of Events (303)

Table 1: Schedule of Assessments

Visit Window	Screen		BL	Double-Blind				
Visit Number	1[1]		2	3	4	5	6	Phone
Day Number	-14	-7	0	7	14	21	28/ET[2]	
Informed Consent	X							
Medical History	X							
Physical Exam[3]	X						X	
Vital Signs[4]	X		X	X	X	X	X	
Hematology	X		X		X		X	
Chemistry	X		X		X		X	
Urinalysis	X		X		X		X	
Lipid panel (fasting)	X		X		X		X	
TSH	X							
CK[5]	X		X		X		X	
Urine Pregnancy Test (if applicable)	X		X				X	
Urine Drug Screen[6]	X							
Electrocardiogram	X		X		X		X	
SCID-I	X							
KBIT	X							
Washout of current ADHD treatment[7]		X						
ADHD-Rating Scale (ADHD-RS)[8]			X	X	X	X	X	
Clinical Global Impression – Severity (CGI-S)			X	X	X	X	X	
Clinical Global Impression – Change (CGI-C)				X	X	X	X	
Clinical Global Impression – Efficacy Index (CGI-E)				X	X	X	X	
HAM-A and Depression HAM-D	X		X		X		X	
Social Adjustment Scale – Self Report (SAS-SR)			X		X		X	
Q-LES-Q			X		X		X	
CAARS-S:S[9]		X	X	X	X	X	X	
Assess Smoking History/Habits[10]			X	X	X	X	X	
Dispense Double-blind Medication[11]			X	X	X	X		
Review Compliance				X	X	X	X	
Assess Adverse Events[12]			X	X	X	X	X	
30-Day Telephone Contact[13]								X

[1] More than one day was allowed for Screening procedures, but all Screening procedures were completed prior to beginning the washout period.
[2] Or early termination (ET).
[3] Physical examination included height and weight. Height was collected at Screening.
[4] Vital signs included blood pressure, pulse, and respiration, performed after the subject has been sitting for at least 5 minutes and done prior to venipuncture for laboratory testing.
[5] Total CK. Isoenzymes were drawn only if there was clinically significant elevations in CK.
[6] Substances of potential abuse, other than stimulant medications prescribed for the treatment of ADHD, were exclusionary.
[7] All screening procedures were completed prior to beginning washout of prior ADHD therapy.
[8] Ratings on the ADHD Rating Scale were provided to the investigator to aid in judging disease severity and change in illness to complete CGI-S and CGI-C ratings respectively. The ADHD Rating Scale was completed by subjects with a clinician with reference to their ADHD symptoms during the week prior.
[9] The CAARS-S:S self-report rating was collected using an interactive voice response system (IVRS) during the 7-day washout period at lunch and dinner-time on Monday, Wednesday and Friday, and during the double-blind period at 4 hours post-dose and 12 hours post-dose on Monday, Wednesday and Friday.
[10] Data regarding the subjects' smoking histories (if applicable) and current smoking habits was collected.
[11] Subjects completed a one-week (7 days) washout of prior ADHD therapy between Visit 1 (Screening) and Visit 2 (Baseline).
[12] AEs were collected from the time of consent. Non-serious AEs were collected through the last day of study medication exposure. SAEs were collected for 30 days post-discontinuation of study medication.
[13] A telephone contact occurred at 30 days respectively, post-discontinuation of study drug. If the subject enrolled into the 12-month open label study (protocol 381.304), this assessment was not to be completed until he/she completed his or her participation in the 381.304 study.

4. Subject Disposition for All Enrolled Subjects (303)

Table 5: Subject Disposition for All Enrolled Subjects

	TPR†	Placebo	ADDERALL XR™ 20 mg	ADDERALL XR™ 40 mg	ADDERALL XR™ 60 mg	Total
Enrolled	4 (100.0%)	64 (100.0%)	66 (100.0%)	64 (100.0%)	61 (100.0%)	259 (100.0%)
Randomized	0 (0.0%)	64 (100.0%)	66 (100.0%)	64 (100.0%)	61 (100.0%)	255 (98.5%)
Completed	0 (0.0%)	42 (65.6%)	47 (71.2%)	49 (76.6%)	45 (73.8%)	183 (70.7%)
Primary reason for discontinuation, n (%)‡						
Adverse event(s)	0 (0.0%)	1 (1.6%)	9 (13.6%)	6 (9.4%)	8 (13.1%)	24 (9.3%)
Protocol violation	3 (75.0%)	1 (1.6%)	1 (1.5%)	1 (1.6%)	0 (0.0%)	6 (2.3%)
Withdrew consent	0 (0.0%)	4 (6.3%)	0 (0.0%)	1 (1.6%)	1 (1.6%)	6 (2.3%)
Lost to follow-up	0 (0.0%)	2 (3.1%)	4 (6.1%)	1 (1.6%)	3 (4.9%)	10 (3.9%)
Lack of efficacy	0 (0.0%)	14 (21.9%)	5 (7.6%)	6 (9.4%)	4 (6.6%)	29 (11.2%)
Other	1 (25.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)

† Terminated prior to randomization

‡ Percentage of the number of enrolled subjects in each treatment group

Source: Section 14, Table 1.2.1

5. Length of Exposure to Study Drug (303)

Table 20: Length of Exposure to Study Drug for All Randomized Subjects

Length of exposure	Placebo (N=64)	ADDERALL XR™ 20 mg (N=66)	ADDERALL XR™ 40 mg (N=64)	ADDERALL XR™ 60 mg (N=61)
1-3 days	1 (1.6%)	0 (0%)	1 (1.6%)	0 (0%)
4-7 days	1 (1.6%)	2 (3.0%)	4 (6.3%)	0 (0%)
2 weeks	8 (12.5%)	7 (10.6%)	2 (3.1%)	7 (11.5%)
3 weeks	10 (15.6%)	6 (9.1%)	5 (7.8%)	6 (9.8%)
4 weeks	14 (21.9%)	14 (21.2%)	11 (17.2%)	10 (16.4%)
5 weeks	29 (45.3%)	35 (53.0%)	41 (64.1%)	37 (60.7%)
6 weeks	1 (1.6%)	2 (3.0%)	0 (0%)	1 (1.6%)

Source: Section 14, Table 3.1.1

6. Extent of Exposure in Multiple Dose Studies

Table 4 Extent of Exposure in Multiple Dose Studies

	Duration of Exposure	Dose of ADDERALL XR®			
		20 mg	40 mg	60 mg	Any Dose[1]
Multiple Dose Studies Combined	< 1 month	109 (54.1%)	103 (49.5%)	50 (34.7%)	37 (14.9%)
	≥ 1 month -<2months	48 (19.4%)	27 (12.6%)	15 (10.4%)	15 (6.0%)
	≥ 2 months -<3months	5 (2.0%)	15 (7.0%)	19 (13.2%)	7 (2.8%)
	≥ 3 months -<6 months	27 (10.9%)	46 (21.5%)	41 (28.5%)	115 (46.4%)
	≥ 6 months	9 (3.6%)	20 (9.3%)	19 (13.2%)	74 (29.8%)
	Total	248	214	144	248
SLI381.303	< 1 week	20 (10.6%)	16 (13.8%)	9 (15.8%)	6 (3.1%)
	≥ 1 week- < 2 weeks	113 (59.2%)	48 (41.5%)	6 (10.5%)	16 (8.4%)
	≥ 2 weeks-< 3 weeks	6 (3.1%)	5 (4.2%)	42 (73.7%)	18 (9.4%)
	≥ 3 weeks-< 4 weeks	6 (3.1%)	47 (39.8%)	0	18 (9.4%)
	≥ 4 weeks	46 (24.1%)	1 (0.8%)	0	133 (69.6%)
	Total	191	118	57	191
SLI381.304	< 1 month	175 (78.5%)	99 (51.6%)	24 (20.5%)	24 (10.8%)
	≥ 1 month- < 2months	8 (3.6%)	16 (8.4%)	15 (12.8%)	10 (4.5%)
	≥ 2 months-<3 months	5 (2.2%)	11 (5.8%)	18 (15.4%)	13 (5.8%)
	≥ 3 months < 6months	28 (12.6%)	46 (24.2%)	41 (35.0%)	116 (52.0%)
	≥ 6 months	7 (3.1%)	19 (10.0%)	19 (16.2%)	60 (26.9%)
	Total	223	190	118	223

[1]Cumulative exposure to any dose

Source: Appendix 1, ISS Table 6.4.2 (Note: Table 6 in Appendix 2, SLI381.304 study report presented the duration of exposure in a slightly different way.)

7. Adverse Events Leading to Termination in > 1 % Randomized Subjects (303)

Table 24: Adverse Events Leading to Termination in >1% of All Randomized Subjects

Body System Preferred Term	Placebo (N=64)	ADDERALL XR™ 20 mg (N=66)	ADDERALL XR™ 40 mg (N=64)	ADDERALL XR™ 60 mg (N=61)
Total†	1 (1.6%)	9 (13.6%)	6 (9.4%)	8 (13.1%)
Insomnia	0 (0.0%)	4 (6.1%)	3 (4.7%)	3 (4.9%)
Nervousness	1 (1.6%)	2 (3.0%)	0 (0.0%)	1 (1.6%)
Anxiety	0 (0.0%)	2 (3.0%)	0 (0.0%)	2 (3.3%)
Agitation	1 (1.6%)	2 (3.0%)	0 (0.0%)	1 (1.6%)
Anorexia	0 (0.0%)	2 (3.0%)	1 (1.6%)	0 (0.0%)
Dry mouth	0 (0.0%)	1 (1.5%)	1 (1.6%)	1 (1.6%)
Tachycardia	0 (0.0%)	2 (3.0%)	0 (0.0%)	1 (1.6%)
Headache	0 (0.0%)	0 (0.0%)	2 (3.1%)	1 (1.6%)

† Subjects may have experienced more than one AE

Source: Section 14, Table 3.2.6

8. Adverse Terms Resulting in Discontinuation (Vignettes: 303)

Vignette Term	Placebo	AXR Total	AXR 20 mg	AXR 40 mg	AXR 60 mg
Insomnia		13	5 (7.8)	4 (6.25)	4 (6.5)
Agitation/Irritability	1	8	4	2	2
Nervous, anxious	1	8	3	1	4
Anorexia, decrease appetite		7	2	4	3
Dry mouth		6	2	1	3
Headache		5	1	2	2
Tachycardia		2	1		1
Asthenia		2	0	2	
Sweating		2		1	1
Vasodilatation/Cold Hands		3	1	1	1
Nausea		2	1	1	
Diarrhea		2	1		1
Dif concentrating, Foggy		2	1		1
Hyperkinesia		2	1		1
Teeth clenching		2		1	1
Myalgia		1			1
Dyspepsia/Indigestion		1		1	
Amnesia, Forgetful		1	1		
Word Finding Difficulty		1			1
Somnolence		1		1	
Amnesia		1			
Stuttering		1	1		
Tremors		1	1		
Thirst		1	1		
Oliguria		1		1	
Weight loss		1		1	
Dizzy		1	1		
Hypertension		1	1		
Chest pain		1		1	
Abdominal Pain		1			1
Dyspnea		1		1	
LFT's Inc		1		1	
Dysmenorrhea		1		1	
Taste perversion		1	1		
Cocaine craving		1	1		

AXR=Adderall XR

9. TEAE's for Randomized Subjects (303)

Table 22: Treatment-Emergent Adverse Events Reported by >5% of Subjects in Any Treatment Group for All Randomized Subjects

Body System Preferred Term	Placebo (N=64)		ADDERALL XR™ 20 mg (N=66)		ADDERALL XR™ 40 mg (N=64)		ADDERALL XR™ 60 mg (N=61)	
	All	Related†	All	Related†	All	Related†	All	Related†
Any AEs	36 (56.3%)	30 (46.9%)	53 (80.3%)	45 (68.2%)	57 (89.1%)	52 (81.3%)	52 (85.2%)	50 (82.0%)
Dry mouth	3 (4.7%)	3 (4.7%)	16 (24.2%)	16 (24.2%)	28 (43.8%)	28 (43.8%)	23 (37.7%)	23 (37.7%)
Anorexia	2 (3.1%)	2 (3.1%)	13 (19.7%)	13 (19.7%)	27 (42.2%)	27 (42.2%)	23 (37.7%)	23 (37.7%)
Headache	8 (12.5%)	8 (12.5%)	12 (18.2%)	9 (13.6%)	20 (31.3%)	19 (29.7%)	18 (29.5%)	16 (26.2%)
Insomnia	8 (12.5%)	8 (12.5%)	17 (25.8%)	14 (21.2%)	19 (29.7%)	19 (29.7%)	16 (26.2%)	16 (26.2%)
Nervousness	8 (12.5%)	8 (12.5%)	7 (10.6%)	7 (10.6%)	10 (15.6%)	10 (15.6%)	7 (11.5%)	7 (11.5%)
Weight loss	0 (0.0%)	0 (0.0%)	3 (4.5%)	3 (4.5%)	10 (15.6%)	10 (15.6%)	7 (11.5%)	7 (11.5%)
Nausea	2 (3.1%)	1 (1.6%)	5 (7.6%)	5 (7.6%)	5 (7.8%)	5 (7.8%)	6 (9.8%)	6 (9.8%)
Urinary tract infection	0 (0.0%)	0 (0.0%)	2 (3.0%)	1 (1.5%)	4 (6.3%)	0 (0.0%)	3 (4.9%)	0 (0.0%)
Asthenia	3 (4.7%)	3 (4.7%)	2 (3.0%)	1 (1.5%)	6 (9.4%)	6 (9.4%)	4 (6.6%)	3 (4.9%)
Agitation	3 (4.7%)	3 (4.7%)	5 (7.6%)	5 (7.6%)	4 (6.3%)	4 (6.3%)	6 (9.8%)	6 (9.8%)
Anxiety	3 (4.7%)	2 (3.1%)	4 (6.1%)	4 (6.1%)	5 (7.8%)	4 (6.3%)	6 (9.8%)	6 (9.8%)
Infection	1 (1.6%)	0 (0.0%)	4 (6.1%)	0 (0.0%)	1 (1.6%)	0 (0.0%)	3 (4.9%)	0 (0.0%)
Diarrhea	0 (0.0%)	0 (0.0%)	5 (7.6%)	4 (6.1)	3 (4.7%)	3 (4.7%)	4 (6.6%)	4 (6.6%)
Constipation	0 (0.0%)	0 (0.0%)	1 (1.5%)	1 (1.5%)	1 (1.6%)	1 (1.6%)	5 (8.2%)	4 (6.6%)
Tachycardia	2 (3.1%)	2 (3.1%)	5 (7.6%)	5 (7.6%)	4 (6.3%)	4 (6.3%)	3 (4.9%)	3 (4.9%)
Dizziness	0 (0.0%)	0 (0.0%)	4 (6.1%)	4 (6.1%)	5 (7.8%)	5 (7.8%)	5 (8.2%)	5 (8.2%)
Rhinitis	4 (6.3%)	1 (1.6%)	2 (3.0%)	0 (0.0%)	3 (4.7%)	0 (0.0%)	2 (3.3%)	0 (0.0%)
Palpitation	0 (0.0%)	0 (0.0%)	5 (7.6%)	5 (7.6%)	2 (3.1%)	2 (3.1%)	1 (1.6%)	1 (1.6%)
Abdominal pain	2 (3.1%)	2 (3.1%)	2 (3.0%)	1 (1.5%)	0 (0.0%)	0 (0.0%)	4 (6.6%)	4 (6.6%)
Pain	3 (4.7%)	1 (1.6%)	2 (3.0%)	0 (0.0%)	4 (6.3%)	0 (0.0%)	4 (6.6%)	2 (3.3%)
Dyspepsia	4 (6.3%)	4 (6.3%)	0 (0.0%)	0 (0.0%)	2 (3.1%)	2 (3.1%)	1 (1.6%)	1 (1.6%)

† Related AEs are those considered possibly or probably related to the study drug.
Source: Section 14, Tables 3.2.3 and 3.2.8

10. Table: Subjects Who Withdrew For Adverse Events (303)

Age	Sex	Race	Dose	Duration	Event	Other Meds	Resolved
44	M	W	PO		Agitation Nervousness	SN	
27	M	W	20 mg	5 d	Insomnia Anorexia Nausea Agitation Thirst	SN	Yes
38	M	W	20 mg	8 d	Cocaine Craving, moderate	SN	Yes
29	F	W	20 mg	8 d	Dry mouth, mild Nervousness, mild Amnesia (forgetfulness), mild Anorexia, mild	SN	Yes
21	F	W	20 mg	16 d	Anxiety, severe Panic attack, mild	SN	Yes
35	M	W	20 mg	17 d	Irritability, severe Watery diarrhea, moderate Vasodilatation, mild Hand tremors, mild Agitation, severe Speech disorder (stuttering), moderate Difficulty concentrating, moderate	SN	Yes
28	M	A	20 mg	22 d	Hypertension (180/82 to138, 92 to 152/104), moderate Tachycardia (106 bpm), moderate Insomnia, moderate to mild	Bupropion	No
51	M	W	20 mg	8 d	Insomnia, severe Taste perversion (metallic taste), mild Dry mouth, mild	SN	Yes
41	M	W	20 mg	4 d	Tachycardia (not recorded), moderate Insomnia, moderate	SN	Yes
43	M	H	20 mg	13 d	Hyperkinesia, moderate Insomnia, moderate Nervousness, mild Headache, moderate Agitation, moderate Dizziness, moderate	SN	No-Other's Yes-Headache

48	M	W	40 mg	20 mg (2 d)	Somnolence, moderate Insomnia, moderate Anorexia, moderate	SN	Yes
34	F	A	40 mg	20 mg (6 d)	Headache, moderate Asthenia, moderate Dysmenorrhea, moderate Nausea, mild	SN	Uncertain- Headache Yes-Other's
57	F	W	40 mg	20 mg (7 d) 40 mg (21 d)	Baseline , borderline transaminase elevation with increase, mild Insomnia, mild Anorexia, mild Dyspepsia, mild Dry mouth, mild	SN	No-Transaminase, anorexia Yes-Other's
44	M	W	40 mg	20 mg (7 d) 40 mg (17 d)	Insomnia, moderate-severe Irritability, moderate-mild Oliguria (decreased urinary flow), mild Agitation, mild Dyspnea, mild Sweating, mild Cold hands, mild	SN	No-insomnia, irritability, Oliguria, sweating, cold Hands Yes-Agitation, dyspnea
41	M	H	40 mg	20 mg (4 d)	Insomnia, severe Dry mouth, mild Asthenia, mild Chest pain, mild Headache, mild Teeth clenching, mild	SN	Yes-headache, chest pain, dry mouth, asthenia, teeth clenching
49	M	W	40 mg	20 mg (7 d) 40 mg	Decreased appetite, moderate Weight loss (6 lbs), moderate	Investigational	No
51	M	W	60 mg	20 mg (7 d) 40 mg (7 d) 60 mg (8 d)	Nervousness, moderate Hyperkinesia, moderate Anorexia, moderate Teeth clenching, moderate Myalgia, mild	SN	No-Nervousness, anorexia, agitation Yes-Hyperkinesia, teeth clenching, myalgia
76	M	W	60 mg	20 mg (7 d) 40 mg (7 d) 60 mg (9 d)	Insomnia, severe Dry mouth	SN	No
34	M	W	60 mg	20 mg (7 d) 40 mg (7 d)	Tachycardia, moderate Sweating, moderate	SN	No-tachycardia, sweating, anxiety

				60 mg (3 d)	Anxiety, moderate Dry mouth, moderate		Yes-Dry mouth
59	F	W	60 mg	20 mg (7 d) 40 mg (7 d) 60 mg (3 d)	Headache, mild Diarrhea Indigestion Dry mouth, mild Nervousness, mild	SN	Yes
29	F	W	60 mg	20 mg (7 d) 40 mg (2 d) 60 mg (3 d)	Depersonalization (foggy), moderate Abnormal thinking (echo in head)	D-amphetamine	Yes
M=Male; F=Female; SN=Stimulant Naïve; White=W; Asian=A; Hispanic=H							

11. ADHD-RS Rating Scale: 18 Item Scale Measures Behaviors of Children with ADHD

Table 2: ADHD-RS Subscales

Subscale	Item
Hyperactivity/Impulsivity	1. Difficulty Remaining Seated 2. Fidgety 3. Difficulty Playing Quietly 4. Talk Excessively 8. Interrupts or Intrudes 9. Blurts Out Answers 10. Difficulty Waiting Turn 17. Often "on the go" or Acts Like "driven by a motor" 18. Hyperactivity/Restlessness
Inattentiveness	5. Difficulty Sustaining Attention 6. Difficulty Following Instructions 7. Easily Distracted 11. Loses Things 12. Doesn't Listen 13. Fails to pay Close Attention to Details 14. Difficulties Organizing 15. Avoidance or Strong Dislike of Mental Tasks 16. Often Forgetful

12. Mean Total ADHD-RS Scores for Placebo and Adderall XR (20, 40, 60 mg) for Four Weeks

Table 8-14 Mean Total ADHD – RS Scores in Patients Treated with Placebo or ADDERALL XR™ for Four Weeks

Week of Treatment		Week 1	Week 2	Week 3	Week 4	
Visit	Baseline	Visit 3	Visit 4	Visit 5	Visit 6	Endpoint
Placebo (N)	60	60	56	45	42	60
Mean ± SD	33.0 ± 6.75	28.3 ± 11.23	28.1 ± 11.52	24.1 ± 10.22	23.2 ± 11.09	26.4 ± 12.24
20 mg (N)	64	64	58	51	47	64
Mean ± SD	31.1 ± 9.61	21.5 ± 11.76†	20.2 ± 11.32‡	18.2 ± 11.28	16.5 ± 11.51	18.5 ± 12.48‡
40 mg (N)	64	64	56	53	50	64
Mean ± SD	31.3 ± 8.13	22.7 ± 9.75*	17.7 ± 9.71‡	16.3 ± 10.36†	16.4 ± 10.79*	18.4 ± 11.5‡
60 mg (N)	60	60	57	49	46	60
Mean ± SD	32.9 ± 9.0	23.6 ± 11.0‖	20.6 ± 12.0‡	17.1 ± 10.0‡	16.3 ± 11.20‖	18.5 ± 11.00‡

Source: Study Report SLI381.303, Section 14, Table 2.1.1.

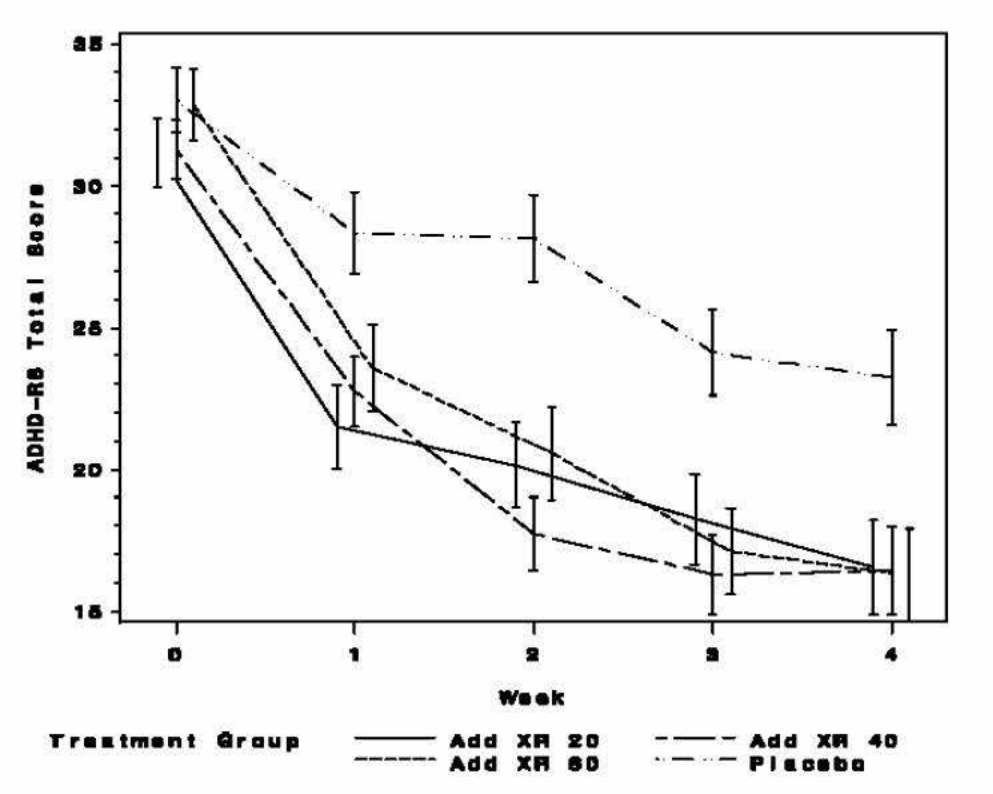
Significantly different from placebo- of the same time point* ≤ 0.05; † ≤ 0.01; ‡ ≤ 0.001

13. Table: ADHD-RS without Items 1, 3, 4 and 9

ADHD-RS Inattentiveness Score – Baseline	**N**	60	64	64	60
	Mean	18.93	17.78	18.02	18.17
	Std	4.81	5.36	5.04	6.09
ADHD-RS Inattentiveness Score – Endpoint	**N**	60	64	64	60
	Mean	14.95	10.69	10.34	10.03
	Std	7.05	7.35	7.31	7.33
	p-value	N/A	0.0054	0.0007	0.0002
ADHD-RS Total – Baseline (excluding items 1,3,4,9)	**N**	60	64	64	60
	Mean	27.57	26.14	26.24	27.05
	Std	6.39	7.48	6.44	7.97
ADHD-RS Total – Endpoint (excluding items 1,3,4,9)	**N**	60	64	64	60
	Mean	21.98	15.76	15.63	15.50
	Std	9.53	10.48	9.73	9.74
	p-value	N/A	0.0022	0.0007	0.0002

Items: # 1: Difficulty Remaining Seated; # 3: Difficulty Playing Quietly; # 4: Talk Excessively; # 9: Blurts Out Answers

14. Figure: Mean ADHD-RS Total Score/Week/Treatment Groups



15. Table: HAM-D at Baseline and Endpoint in ITT (303)

Table 18: Summary of HAM-D at Baseline and Endpoint for the ITT Population

	Placebo	ADDERALL XR™ 20 mg	ADDERALL XR™ 40 mg	ADDERALL XR™ 60 mg
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
N	60	64	64	60
Baseline	4.2 (2.85)	3.9 (2.78)	4.4 (2.97)	4.0 (2.98)
N	60	63	62	58
Endpoint	3.0 (2.80)	3.2 (2.88)	4.5 (4.08)	3.9 (4.24)
p value†	NA‡	0.667	0.018*	0.049*

* Indicates statistical significance, p<0.050
† Dunnett's test was used in the construction of p values
‡ Not applicable
Source: Section 14, Table 2.14.1

16. Table: HAM-A at Baseline and Endpoint in ITT (303)

Table 19: Summary of HAM-A at Baseline and Endpoint for the ITT Population

	Placebo	ADDERALL XR™ 20 mg	ADDERALL XR™ 40 mg	ADDERALL XR™ 60 mg
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
N	60	64	64	60
Baseline	6.3 (3.58)	6.3 (3.18)	6.2 (3.47)	6.0 (3.37)
N	60	63	62	58
Endpoint	4.6 (3.57)	4.7 (3.65)	6.3 (4.77)	6.1 (4.97)
p value†	NA‡	0.924	0.017*	0.010*

* Indicates statistical significance. p<0.050
† Dunnett's test was used in the construction of p values
‡ Not applicable
Source : Section 14. Table 2.15.1

17. Table(s) of Clinical Studies:

Protocol #/ # Study Sites or PIs /Phase/ Publications	Study Design[1]	Study Location and Drug Product Code	Treatment Dose	Randomized *Patients/* Subjects in Each Study	Treatment Duration	Mean Age (Range)	Gender (M%/F %) Race (%)[2]	Study Status Start Date[3]
			Controlled Clinical Studies					
SLI381.303 Phase 3 None	R, DB, PC, PG, MC, MD	United States ADDERALL XR	Once per day: 20mg (2x10 mg) 40 mg (2x20 mg) 60 mg (2x30 mg) Placebo	255 adult patients with ADHD	4 weeks[4]	39.1 (18-76)	60.4%/39.6% White 88.2% Black 3.5% Hispanic 5.5% Asian/Pac. 1.6% Nat. Amer. 0.8% Other 0.4%	Complete 6 Feb02
			Uncontrolled Clinical Studies					
SLI381.304 Phase 3 None	UC, OL, MC, MD	United States ADDERALL XR	Once per day: 20 mg (2x10 mg) 40mg (2x20 mg) 60 mg (2x30 mg) depending on response and tolerability	Up to 200 adult patients with ADHD	Up to 12 months	39.8 (18-76)	59.2%/40.8% White 90.6% Black 2.7% Hispanic 4.9% Asian/Pac. 0.9% Nat. Amer. 0.9%	Ongoing 8 March 02

[1]AC=active controlled; CO=crossover, DB=double-blind; MC=multi-center; MD=multiple dose; SD=single dose; OL=open-label; PC=placebo controlled; PG=parallel group; R=randomized; SC=single center; UC=uncontrolled.
[2]Demographics percentages may not add to 100% due to rounding.
[3]Study start date reflects the date the first patient signed the consent form.
[4]Patients assigned to 40 mg received 20 mg/day during the first week of treatment and 40 mg/day during the remaining weeks; patients assigned to 60 mg/day received 20 mg/day during week 1, 40 mg/day during week 2 and 60 mg/day mg during weeks 3 and 4.

Table 8-2 Table of All Clinical Studies by Indication and Clinical Phase

Protocol#/ #Study Sites or PIs / Phase/ Publications	Study Design[1]	Study Location and Drug Product Code	Treatment Dose	Patients/ Subjects in Each Study	Treatment Duration	Mean Age (Range)	Gender (M%/F%) Race (%)[2]	Study Status Start Date[3]	Location of Final Study Report/ Data Listings
Clinical Pharmacology: Clinical Pharmacokinetics/Bioequivalence									
(b) (4) (b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
381.108 James C. Kisicki, M.D. Phase 1 None	OL, SD, R three – period crossover	United States ADDERALL XR®	2 x 10 mg; fasted 2 x 20 mg, fasted 2 x 30 mg, fasted	12 healthy adult subjects	single-dose, minimum 7-day washout between doses	32.5 (22-46)	41.7%/58.3% Cauc. 100%	Complete 6 July 02	Vols. 2.17-2.18 pg. 6- 1881 Vols. 2.9-2.10 pg. 6-879

[1]AC=active controlled; CO=crossover; DB=double-blind; MC=multicenter; MD=multiple dose; SD=single dose; OL=open-label; PC=placebo controlled; PG=parallel group; R=randomized; SC=single center; UC=uncontrolled.
[2]Demographics percentages may not add to 100% due to rounding.
[3]Study start date reflects the date the first patient signed the consent form.
[4] Patients assigned to 40 mg received 20 mg/ day during the first week of treatment and 40 mg/day during the remaining weeks; patients assigned to 60 mg/day received 20 mg/day during week 1, 40 mg/day during week 2 and 60 mg/day mg during weeks 3 and 4.

Table 8-3 Table of All Clinical Studies by Indication and Clinical Phase (cont.)

Protocol#/ #Study Sites or PIs / Phase/ Publications	Study Design[1]	Study Location and Drug Product Code	Treatment Dose	Patients/ Subjects in Each Study	Treatment Duration	Mean Age (Range)	Gender (M%/F%) Race (%)[2]	Study Status Start Date[3]	Location of Final Study Report/ Data Listings
Clinical Pharmacology: Clinical Pharmacokinetics/Bioequivalence (cont.)									
SLI381.102 Phase 1 None	OL, SD, R Five-period crossover	United States ADDERALL®	Part 1 1 x 20 mg of three different formulations or 2 x 10 mg (4 hrs apart) with food. Part 2 1 x 20 mg after 10 hr fast	20 healthy adult subjects	Single dose, minimum 7 day washout between each treatments	40 (23-55)	65%/35% Cauc. 85% Black 10% Other 5%	Complete 28 April 99	Original NDA (21-303) Vols. 1.45-1.48
SLI381.103 Phase 1 None	OL, SD, R Three period crossover	United States ADDERALL XR®	1 x 30 mg fasted 1 x 30 mg with high fat breakfast 1 x 30 mg sprinkled on applesauce	21 healthy adult subjects	Single dose, minimum 7 day washout between treatments	35 (20-53)	52%/48% Cauc. 81% Black 10% Hispanic 8% Amer. Ind. 5%	Complete 1 Dec 99	Original NDA (21-303) Vols. 1.49-1.50
SLI381.105 Phase 1 None	OL, MD, Single period	United States ADDERALL XR®	Once per day 1 x 30 mg	20 healthy adult subjects	7 days; final dose was administered under fasting conditions	32 (18-55)	50%/50% Cauc. 70% Black 15% Hispanic 10%	Complete 21 June 00	Original NDA (21-303) Vols. 1.54-1.55

[1]AC=active controlled; CO=crossover; DB=double-blind; MC=multicenter; MD=multiple dose; SD=single dose; OL=open-label; PC=placebo controlled; PG=parallel group; R=randomized; SC=single center; UC=uncontrolled.
[2]Demographics percentages may not add to 100% due to rounding.
[3]Study start date reflects the date the first patient signed the consent form.
[4] Patients assigned to 40 mg received 20 mg/ day during the first week of treatment and 40 mg/day during the remaining weeks; patients assigned to 60 mg/day received 20 mg/day during week 1, 40 mg/day during week 2 and 60 mg/day mg during weeks 3 and 4.

18. DSM-IV-TR Diagnostic Criteria for ADHD

Either (1) or (2):

(1) Six (or more) of the following symptoms of **inattention** have persisted for at least 6 months to a degree that is maladaptive and inconsistent with developmental level:

Inattention

(a) Often fails to give close attention to details or makes careless mistakes in schoolwork, work, or other activities.
(b) Often has difficulty sustaining attention in tasks or play activities.
(c) Often does not seem to listen when spoken to directly.
(d) Often does not follow through on instructions and fails to finish schoolwork, chores, or duties in the workplace (not due to oppositional behavior or failure to understand instructions).
(e) Often has difficulty organizing tasks and activities.
(f) Often avoids, dislikes, or is reluctant to engage in tasks that require sustained mental effort (such as schoolwork or homework).
(g) Often loses things necessary for tasks or activities (e.g., toys, school assignments, pencils, books, or tools).
(h) Is often easily distracted by extraneous stimuli.
(i) Is often forgetful in daily activities.

(2) Six (or more) of the following symptoms of **hyperactivity-impulsivity** have persisted for at least 6 months to a degree that is maladaptive and inconsistent with developmental level:

Hyperactivity

(a) Often fidgets with hands or squirms in seat.
(b) Often leaves seat in classroom or in other situations in which remaining seated is expected.
(c) Often runs about or climbs excessively in situations in which it is inappropriate (in adolescents or adults, may be limited to subjective feelings of restlessness).
(d) Often has difficulty playing or engaging in leisure activities quietly.
(e) Is often "on the go" or often acts as if "driven by a motor".
(f) Often talks excessively.

Impulsivity

(a) Often blurts out answers before questions have been completed.
(b) Often has difficulty awaiting turn.
(c) Often interrupts or intrudes on others (e.g., butts into conversations or games).

B. Some hyperactive-impulsive or inattentive symptoms that caused impairment were present before the age of 7 years.

C. Some impairment from the symptoms is present in two or more settings (e.g., at school and at home)

19. Schedule of Assessments (Study 304):

Table 1. Schedule of Assessments

Visit Window	± 2 days					± 7 days										
Visit Number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16/ET[1]
Week/Month Number	BL[2]	W 1	W 2	W 3	W 4/M 1	M 2	M 3	M 4	M 5	M 6	M 7	M 8	M 9	M 10	M 11	M 12/ET
Informed Consent	X															
Medical History	X[3]															
Physical Exam[4]	X															X
Vital Signs[5]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hem/Chem/Urinalysis	X		X		X		X			X						X
Lipids[6]	X		X		X		X			X						X
CK[7]	X		X		X		X			X						X
Urine Pregnancy Test	X															X
12-lead Electrocardiogram	X		X		X		X			X						X
ADHD Rating Scale	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
SASSR	X									X						X
Q-LES-Q	X									X						X
Assess Smoking History[8]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Dispense Medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Assess AEs[9]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Review Compliance		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
30 Day Phone Contact																X[10]

[1] Or early termination.
[2] Corresponds to the last visit of double-blind study.
[3] Medical history from the double-blind protocol 381.303 was reviewed. Any ongoing AEs from protocol 381.303 were recorded in medical history.
[4] Physical examination includes weight.
[5] Vital signs include blood pressure, pulse, and respiration. All vitals are performed after the subject has been sitting for at least 5 minutes and should precede, not follow venipuncture for laboratory testing.
[6] Lipid panel must be done with the subject fasting.
[7] Isoenzymes will be drawn for clinically significant elevations in CK.
[8] Data regarding the subjects smoking history (if applicable) and current smoking habits will be collected.
[9] AEs were collected from time of consent. Non-serious AEs will be collected through to the last day of study drug. SAEs will be collected for 30 days post-discontinuation of study drug.
[10] A telephone contact will occur at 30 (+/- 7) days post-discontinuation of study drug.

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20. Baseline Demographics (Study 304)

Table 5: Summary of Subject Demographic Characteristics and Baseline Information for the ITT Population

		Placebo	ADDERALL XR ™ Without Interruption	ADDERALL XR™ With Interruption	Total
Age (Years)	N	56	144	21	221
	Mean (SD)	39.9 (11.40)	39.3 (11.28)	42.6 (12.86)	39.8 (11.45)
	Median	39.0	39.0	43.0	39.0
	Min, Max	19, 59	18, 68	21, 76	18, 76
Age Category (Years)	18-29	12 (21.4%)	34 (23.6%)	3 (14.3%)	49 (22.2%)
	30-39	17 (30.4%)	43 (29.9%)	6 (28.6%)	66 (29.9%)
	40-49	15 (26.8%)	38 (26.4%)	5 (23.8%)	58 (26.2%)
	≥ 50	12 (21.4%)	29 (20.1%)	7 (33.3%)	48 (21.7%)
Gender	Male	37 (66.1%)	82 (56.9%)	12 (57.1%)	131 (59.3%)
	Female	19 (33.9%)	62 (43.1%)	9 (42.9%)	90 (40.7%)
Ethnic Origin	White	52 (92.9%)	129 (89.6%)	19 (90.5%)	200 (90.5%)
	Black	2 (3.6%)	3 (2.1%)	1 (4.8%)	6 (2.7%)
	Hispanic	2 (3.6%)	8 (5.6%)	1 (4.8%)	11 (5.0%)
	Asian/Pacific Islander	0 (0.0%)	2 (1.4%)	0 (0.0%)	2 (0.9%)
	Native American	0 (0.0%)	2 (1.4%)	0 (0.0%)	2 (0.9%)
	Other	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Weight (lb)	N	55	144	21	220
	Mean (SD)	185.7 (46.53)	177.4 (38.60)	172.3 (40.36)	179.2 (40.94)
	Median	196.0	176.0	176.0	178.0
	Min, Max	100, 296	94, 317	93, 228	93, 317

Source: Section 14, Table 1.3.2

21. TEAE's Reported by 5 % of All Subjects (304)

Table 11: Treatment-Emergent Adverse Events Reported by ≥5% of All Enrolled Subjects

Preferred Term	ADDERALL XR® 20 mg† (N=223)		ADDERALL XR® 40 mg† (N=190)		ADDERALL XR® 60 mg† (N=117)		Total (N=223) *	
	All	Related‡	All	Related‡	All	Related‡	All	Related‡
Total	151 (67.7%)	129 (57.8%)	125 (65.8%)	96 (50.5%)	91 (77.8%)	75 (64.1%)	267 (82.0%)	181 (81.2%)
Dry mouth	64 (28.7%)	63 (28.3%)	22 (11.6%)	22 (11.6%)	17 (14.5%)	17 (14.5%)	94 (42.2%)	93 (41.7%)
Anorexia	47 (21.1%)	47 (21.1%)	13 (6.8%)	13 (6.8%)	12 (10.3%)	11 (9.4%)	67 (30.0%)	66 (29.6%)
Insomnia	30 (13.5%)	28 (12.6%)	18 (10.0%)	18 (9.5%)	16 (13.7%)	16 (13.7%)	58 (26.5%)	57 (25.6%)
Headache	22 (9.9%)	15 (6.7%)	17 (8.9%)	12 (6.3%)	15 (12.8%)	11 (9.4%)	50 (22.4%)	36 (16.1%)
Nervousness	21 (9.4%)	21 (9.4%)	17 (8.9%)	15 (7.9%)	15 (12.8%)	15 (12.8%)	46 (20.6%)	43 (19.3%)
Infection	11 (4.9%)	0 (0.0%)	7 (3.7%)	0 (0.0%)	6 (5.1%)	0 (0.0%)	24 (10.8%)	0 (0.0%)
Weight loss	12 (5.4%)	12 (5.4%)	7 (3.7%)	7 (3.7%)	6 (5.1%)	5 (4.3%)	23 (10.3%)	22 (9.9%)
Nausea	6 (2.7%)	6 (2.7%)	10 (5.3%)	7 (3.7%)	5 (4.3%)	3 (2.6%)	21 (9.4%)	16 (7.2%)
Anxiety	8 (3.6%)	7 (3.1%)	8 (4.2%)	7 (3.7%)	6 (5.1%)	3 (2.6%)	21 (9.4%)	17 (7.6%)
Dizziness	3 (1.3%)	3 (1.3%)	10 (5.3%)	9 (4.7%)	9 (7.7%)	9 (7.7%)	21 (9.4%)	20 (9.0%)
Agitation	11 (4.9%)	11 (4.9%)	7 (3.7%)	7 (3.7%)	7 (6.0%)	7 (6.0%)	20 (9.0%)	20 (9.0%)
Asthenia	12 (5.4%)	9 (4.0%)	5 (2.6%)	4 (2.1%)	2 (1.7%)	1 (0.9%)	18 (8.1%)	13 (5.8%)
Depression	10 (4.5%)	8 (3.6%)	4 (2.1%)	1 (0.5%)	1 (0.9%)	0 (0.0%)	15 (6.7%)	9 (4.0%)
Pain	7 (3.1%)	2 (0.9%)	2 (1.1%)	0 (0.0%)	5 (4.3%)	2 (1.7%)	14 (6.3%)	4 (1.8%)
Constipation	6 (2.7%)	6 (2.7%)	3 (1.6%)	3 (1.6%)	6 (5.1%)	5 (4.3%)	14 (6.3%)	13 (5.8%)
Hypertonia§	4 (1.8%)	4 (1.8%)	4 (2.1%)	4 (2.1%)	6 (5.1%)	5 (4.3%)	14 (6.3%)	13 (5.8%)
Myalgia	6 (2.7%)	3 (1.3%)	2 (1.1%)	0 (0.0%)	4 (3.4%)	1 (0.9%)	12 (5.4%)	4 (1.8%)

† Dose at onset of AE

‡ Related AEs are those considered possibly related or related to the study drug

§ AEs involving muscle clenching, spasm and stiffness; no upper motor neuron signs were seen.

* In Total column subjects are only counted once for each individual adverse event, regardless of whether it was reported at more than one dose.

Source: Section 14, Tables 3.6.6 and 3.3.6

22. Table 8: AE's ≥ 2 % of Subjects (Study 303)

Table 8 Adverse Events in the Controlled Multiple Dose Study Reported by Greater Than or Equal to 2% of Subjects in ADDERALL XR® Group

	SLI381.303			
	Placebo (N = 64)		ADDERALL XR® (N=191)	
BODY SYSTEM Preferred Term	Number (%) of Subjects Reporting	Number of AEs	Number (%) of Subjects Reporting	Number of AEs
ANY ADVERSE EVENT	36 (56.3%)	104	162 (84.8%)	683
BODY AS A WHOLE	16 (25.0%)	27	80 (41.9%)	133
Abdominal Pain	2 (3.1%)	2	6 (3.1%)	6
Asthenia	3 (4.7%)	3	12 (6.3%)	14
Headache	8 (12.5%)	10	50 (26.2%)	66
Infection	1 (1.6%)	1	8 (4.2%)	9
Pain	3 (4.7%)	3	10 (5.2%)	10
Photosensitivity Reaction	0 (0.0%)	0	5 (2.6%)	5
CARDIOVASCULAR SYSTEM	2 (3.1%)	6	26 (13.6%)	30
Palpitation	0 (0.0%)	0	8 (4.2%)	10
Tachycardia	2 (3.1%)	6	12 (6.3%)	12
DIGESTIVE SYSTEM	13 (20.3%)	19	112 (58.6%)	195
Anorexia	2 (3.1%)	2	63 (33.0%)	63
Constipation	0 (0.0%)	0	7 (3.7%)	8
Diarrhea	0 (0.0%)	0	12 (6.3%)	12
Dry Mouth	3 (4.7%)	3	67 (35.1%)	72
Nausea	2 (3.1%)	2	16 (8.4%)	17
Tooth Disorder	1 (1.6%)	1	5 (2.6%)	5
METABOLIC/NUTRITIONAL	0 (0.0%)	0	27 (14.1%)	33
Weight Loss	0 (0.0%)	0	20 (10.5%)	20

Source: Appendix 1, ISS Table 8.5.4

Table 8 Adverse Events in the Controlled Multiple Dose Study (cont.)

	SLI381.303			
	Placebo (N = 64)		ADDERALL XR® (N=191)	
BODY SYSTEM Preferred Term	Number (%) of Subjects Reporting	Number of AEs	Number (%) of Subjects Reporting	Number of AEs
MUSCULOSKELETAL SYSTEM	2 (3.1%)	2	10 (5.2%)	12
Myalgia	1 (1.6%)	1	4 (2.1%)	4
Twitching	0 (0.0%)	0	5 (2.6%)	5
NERVOUS SYSTEM	21 (32.8%)	41	98 (51.3%)	202
Agitation	3 (4.7%)	3	15 (7.9%)	18
Anxiety	3 (4.7%)	3	15 (7.9%)	18
Depression	2 (3.1%)	2	6 (3.1%)	6
Dizziness	0 (0.0%)	0	14 (7.3%)	16
Emotional Lability	1 (1.6%)	1	5 (2.6%)	5
Hyperkinesia	2 (3.1%)	2	7 (3.7%)	8
Insomnia	8 (12.5%)	9	52 (27.2%)	67
Libido Decreased	0 (0.0%)	0	7 (3.7%)	7
Nervousness	8 (12.5%)	8	24 (12.6%)	28
Somnolence	1 (1.6%)	2	6 (3.1%)	6
Speech Disorder	0 (0.0%)	0	4 (2.1%)	4
RESPIRATORY SYSTEM	5 (7.8%)	6	20 (10.5%)	22
Dyspnea	0 (0.0%)	0	5 (2.6%)	6
Rhinitis	4 (6.3%)	4	7 (3.7%)	7
SKIN/APPENDAGES	1 (1.6%)	1	11 (5.8%)	14
Sweating	0 (0.0%)	0	5 (2.6%)	5
SPECIAL SENSES	1 (1.6%)	1	9 (4.7%)	11
UROGENITAL SYSTEM	1 (1.6%)	1	24 (12.6%)	30
Dysmenorrhea	0 (0.0%)	0	4 (2.1%)	4
Impotence	0 (0.0%)	0	4 (2.1%)	5
Urinary Tract Infection	0 (0.0%)	0	9 (4.7%)	9

Source: Appendix 1, ISS Table 8.5.4

23. Table 9: AE's ≥ 2 % of Subjects (Study 304)

Table 9 Adverse Events in the Uncontrolled Multiple Dose Study Reported by Greater Than or Equal to 2% of Subjects

	SLI381.304: ADDERALL XR®			
	Original sNDA (N = 223)		Current Update (N=223)	
BODY SYSTEM Preferred Term	Number (%) of Subjects Reporting	Number of AEs	Number (%) of Subjects Reporting	Number of AE
ANY ADVERSE EVENT	203 (91.0%)	914	207 (92.8%)	1022
BODY AS A WHOLE				
Abdominal Pain	103 (46.2%)	175	104 (46.6%)	195
Accidental Injury	4 (1.8%)	4	4 (1.8%)	4
Allergic Reaction	6 (2.7%)	8	10 (4.5%)	12
Asthenia	5 (2.2%)	5	6 (2.7%)	7
Back Pain	16 (7.2%)	19	18 (8.1%)	21
Chest Pain	6 (2.7%)	7	7 (3.1%)	8
Headache	5 (2.2%)	5	5 (2.2%)	5
Infection	47 (21.1%)	54	50 (22.4%)	63
Pain	22 (9.9%)	28	24 (10.8%)	31
	18 (8.1%)	21	14 (6.3%)	18
CARDIOVASCULAR SYSTEM				
Hypertension	25 (11.2%)	32	26 (11.7%)	35
Palpitation	4 (1.8%)	4	5 (2.2%)	5
Tachycardia	8 (3.6%)	9	8 (3.6%)	9
	6 (2.7%)	7	6 (2.7%)	7
DIGESTIVE SYSTEM				
Anorexia	136 (61.0%)	252	137 (61.4%)	254
Constipation	66 (29.6%)	73	67 (30.0%)	74
Diarrhea	14 (6.3%)	16	14 (6.3%)	16
Dry Mouth	5 (2.2%)	5	5 (2.2%)	5
Dyspepsia	94 (42.2%)	106	94 (42.2%)	107
Nausea	5 (2.2%)	5	5 (2.2%)	6
	21 (9.4%)	21	21 (9.4%)	21
METABOLIC/NUTRITIONAL				
Weight Loss	27 (12.1%)	33	32 (14.3%)	38
	20 (9.0%)	23	23 (10.3%)	26
HEMIC/LYMPHATIC	3 (1.3%)	3	5 (2.2%)	5

Source: ISS Table 8.5.4 of the original sNDA (Section 8.8.17.2) and the current update (Appendix 4)

Table 9 Adverse Events in the Uncontrolled Multiple Dose Study (cont.)

	NI 181 204: ADDERALL XR®			
	Original sNDA (N = 223)		Current Update (N=223)	
BODY SYSTEM Preferred Term	Number (%) of Subjects Reporting	Number of AEs	Number (%) of Subjects Reporting	Number of AEs
MUSCULOSKELETAL SYSTEM	11 (4.9%)	12	23 (10.3%)	26
Myalgia	5 (2.2%)	5	12 (5.4%)	13
Twitching	3 (1.3%)	3	5 (2.2%)	5
NERVOUS SYSTEM	131 (58.7%)	286	135 (60.5%)	323
Agitation	17 (7.6%)	26	20 (9.0%)	29
Anxiety	19 (8.5%)	22	21 (9.4%)	25
Depression	11 (4.9%)	12	15 (6.7%)	17
Dizziness	20 (9.0%)	25	21 (9.4%)	26
Hyperkinesia	8 (3.6%)	9	9 (4.0%)	10
Hypertonia	12 (5.4%)	14	14 (6.3%)	17
Insomnia	56 (25.1%)	69	59 (26.5%)	74
Libido Decreased	8 (3.6%)	9	8 (3.6%)	9
Nervousness	41 (18.4%)	52	46 (20.6%)	60
Somnolence	5 (2.2%)	5	5 (2.2%)	5
Thinking Abnormal	6 (2.7%)	6	8 (3.6%)	8
Tremor	5 (2.2%)	5	6 (2.7%)	7
RESPIRATORY SYSTEM	27 (12.1%)	33	32 (14.3%)	43
Cough Increased	5 (2.2%)	5	5 (2.2%)	5
Pharyngitis	8 (3.6%)	8	10 (4.5%)	11
Rhinitis	7 (3.1%)	7	10 (4.5%)	11
SKIN/APPENDAGES	22 (9.9%)	29	29 (13.0%)	38
Contact Dermatitis	4 (1.8%)	4	7 (3.1%)	7
Rash	5 (2.2%)	7	6 (2.7%)	8
Sweating	5 (2.2%)	5	5 (2.2%)	5
SPECIAL SENSES	11 (4.9%)	14	14 (6.3%)	17
UROGENITAL SYSTEM	34 (15.2%)	44	37 (16.6%)	47
Urinary Tract Infection	5 (2.2%)	5	7 (3.1%)	7
Urination Impaired	6 (2.7%)	6	6 (2.7%)	6

Source: ISS Table 8.5.4 of the original sNDA (Section 3.8.17.2) and the current update (Appendix 1).

24. Subjects Who Withdrew From Study 303 and 304

Table 16 Patients Discontinued from Study Medication Because of an Adverse Event

Study Medication	Study Number/ Subject ID	Age (yrs)	Sex	Final Dose (mg)	Week Exit	Principal Adverse Event(s) for Discontinuation (Verbatim Term)
			STUDY 381-303 Placebo Group N = 84			
Placebo	381.303/129-030	44	Male	0	2	FELT SPED UP
			ADDERALL XR® Group N = 191			
ADDERALL XR®	381.303/103-104	27	Female	20	2	INSOMNIA
	381.303/103-111	51	Male	60	4	NERVOUS
	381.303/104-003	76	Male	60	4	INSOMNIA
	381.303/104-011	34	Male	60	4	RACING HEART
	381.303/106-009	59	Female	40	2	HEADACHE
	381.303/113-011	48	Male	20	2	SOMNOLENCE
	381.303/115-003	38	Male	20	2	MEDICATION MADE PT CRAVE COCAINE
	381.303/115-004	34	Female	20	2	HEADACHE
	381.303/115-008	29	Female	20	2	TENSION
	381.303/116-005	29	Female	40	3	FOGGY DRUGGED FEELING
	381.303/117-003	21	Female	20	4	ANXIETY
	381.303/121-004	37	Male	40	3	ANXIETY
	381.303/122-008	57	Female	40	4	ELEVATED ALT
	381.303/124-001	44	Male	60	4	AGITATION
	381.303/124-003	35	Male	20	3	IRRITABILITY
	381.303/124-006	44	Male	40	4	INSOMNIA INCREASE
	381.303/124-009	41	Male	20	2	CHEST PAIN
	381.303/124-011	28	Male	20	4	ELEVATED BLOOD PRESSURE
	381.303/124-019	51	Male	20	2	INSOMNIA
	381.303/129-020	41	Male	20	1	HEART RACING
	381.303/129-037	43	Male	20	3	JITTERY
	381.303/130-001	49	Female	20	2	WEIGHT LOSS
	381.303/130-014	50	Female	40	3	INSOMNIA

Source: Appendix 1, ISS Table 8.7.2

Table 16 Patients Discontinued from Study Medication Because of an Adverse Event (cont.)

Study Medication	Study Number/ Subject ID	Age (yrs)	Sex	Final Dose (mg)	Week Exit	Principal Adverse Event(s) for Discontinuation (Verbatim Term)
STUDY SLI381.304 ADDERALL XR® Group N =223						
Discontinuations Reported in the Original sNDA						
ADDERALL XR®	381.304/102-015	40	Female	60	10	PNEUMOENCEPHALOCELE
	381.304/104-015	25	Female	20	2	GASTROENTERITIS
	381.304/106-009	59	Female	20	1	HEADACHE
	381.304/112-007	40	Male	40	9	ANXIETY
	381.304/112-023	29	Male	40	9	INCREASED LIVER ENZYMES
	381.304/113-003	46	Male	20	17	INSOMNIA
	381.304/113-010	48	Female	40	14	HEART PALPITATIONS
	381.304/115-008	29	Female	20	2	TENSION
	381.304/116-001	57	Male	20	3	HEADACHES
	381.304/116-010	57	Female	20	1	DRY MOUTH
	381.304/117-004	49	Male	40	4	ANXIETY
	381.304/117-011	39	Male	40	3	HIGH BLOOD PRESSURE
	381.304/124-011	28	Male	20	15	WORSENING OF ELEVATED BLOOD PRESSURE
	381.304/126-004	25	Female	20	6	WEIGHT LOSS
	381.304/126-006	62	Male	20	7	DECREASED APPETITE
	381.304/128-005	46	Male	40	5	DELAY WITH URINATION
	381.304/128-006	44	Female	40	4	DEPRESSION
	381.304/129-012	19	Female	40	0	WORSENING OF DEPRESSED MOOD
	381.304/129-023	25	Male	20	2	INSOMNIA
	381.304/130-001	49	Female	20	2	INCREASE IN FREQUENCY OF INTERMITTENT INSOMNIA
	381.304/130-008	21	Male	20	3	WEIGHT LOSS

Source: Appendix 1, ISS Table 8.7.2

Table 16 Patients Discontinued from Study Medication Because of an Adverse Event (cont.)

Study Medication	Study Number/ Subject ID	Age (yrs)	Sex	Final Dose (mg)	Week Exit	Principal Adverse Event(s) for Discontinuation (Verbatim Term)
STUDY SLI381.304 ADDERALL XR® Group N =223						
Discontinuations after the Submission of the Original sNDA						
ADDERALL XR®	381.304/102-012	39	Female	60	17	PANIC FEELING
	381.304/102-021	38	Male	20	15	DELUSIONAL THINKING
	381.304/103-111	51	Male	20	25	ANXIETY
	381.304/104-040	48	Female	20	24	DEPRESSION
	381.304/112-024	50	Female	20	22	INSOMNIA
	381.304/113-005	51	Female	60	26	HYPERTENSION
	381.304/115-012	35	Female	20	25	HEADACHE
	381.304/116-007	24	Female	40	25	WEIGHT LOSS
	381.304/121-004	37	Male	20	22	DEPRESSION
	381.304/124-003	35	Male	20	27	DEPRESSION
	381.304/124-006	44	Male	40	31	INTERMITTENT INSOMNIA
	381.304/124-012	44	Male	20	17	IRRITABILITY
	381.304/128-003	40	Male	60	19	NEW ONSET DEPRESSION
	381.304/128-009	35	Female	40	30	PREGNANCY
	381.304/129-031	45	Male	20	16	IRRITABILITY
	381.304/130-014	50	Female	20	22	DEPRESSION

Source: Appendix 1, ISS Table 8.7.2

25. Summary of Drug Exposure for All Exposed Subjects

Table 8: Summary of Drug Exposure for All Exposed Subjects

		ADDERALL XR™ 20 mg	ADDERALL XR™ 40 mg	ADDERALL XR™ 60 mg	Any Dose Level
Length of Exposure (Days)	N	223	190	116	223
	Mean (SD)	24.5 (33.78)	42.2 (39.21)	62.6 (38.74)	92.9 (36.53)
	Median	7.0	21.5	69.0	92.0
	Min, Max	5, 148	1, 178	1, 164	5, 185
Length of Exposure Category (Months)	1	179 (80.3%)	104 (54.7%)	33 (28.4%)	25 (11.2%)
	2	10 (4.5%)	19 (10.0%)	14 (12.1%)	11 (4.9%)
	3	11 (4.9%)	40 (21.1%)	41 (35.3%)	52 (23.3%)
	4-6	23 (10.3%)	27 (14.2%)	28 (24.1%)	133 (59.6%)
	7-9	0 (0%)	0 (0%)	0 (0%)	2 (0.9%)
	10-12	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	> 12	0 (0%)	0 (0%)	0 (0%)	0 (0%)

Source: Section 14, Table 3.1.1

26. ADHD-RS Total (304)

Table 6: ADHD-RS Total Score at Baseline and Endpoint for the ITT Population

		Rollover from Protocol 381.303			Total
		Placebo	ADDERALL XR™ Without Interruption	ADDERALL XR™ With Interruption	
Baseline	N	56	144	21	221
	Mean (SD)	26.5 (12.51)	17.9 (11.60)	19.7 (11.45)	20.2 (12.34)
Endpoint	N	56	144	21	221
	Mean (SD)	14.6 (10.35)	11.9 (9.26)	12.1 (10.17)	12.6 (9.66)
	Change† (SD)	-11.9 (13.52)	-6.0 (10.51)	-7.6 (15.90)	-7.6 (12.12)
	p value‡	< 0.001*	< 0.001*	0.041*	<0.001*

† Change from baseline to endpoint

‡ P value is based on a one sample t-test of change from baseline

Source: Section 14, Table 2.1.1

27. Mean ECG Changes (303, 304)

Table 23 Mean Changes in ECG Parameters for Subjects in SLI381.303

	ADDERALL XR®				Placebo				
Study 381.303	Baseline	Endpoint Actual[1]	Change	%Change	Baseline	Endpoint Actual[1]	Change	%Change	P-Value[2]
PR (msec)									
N	191	182	182	182	64	59	59	59	0.2158
Mean	150.9	148.6	-2.0	-1.1	156.0	157.0	-0.7	-0.2	
SD	18.77	20.48	14.27	9.51	21.10	21.23	12.29	7.92	
QRS (msec)									
N	191	182	182	182	64	59	59	59	0.4464
Mean	88.2	88.8	0.7	1.2	90.0	90.5	0.3	0.0	
SD	6.74	6.73	7.22	8.32	6.76	6.94	6.61	7.23	
QT (msec)									
N	191	182	182	182	64	59	59	59	0.0015
Mean	377.2	368.7	-8.3	-2.0	372.6	375.8	2.9	1.0	
SD	26.51	26.87	22.44	5.87	26.10	24.89	22.12	6.13	
QTc (msec)									
N	191	182	182	182	64	59	59	59	0.0006
Mean	399.9	399.1	4.9	1.3	389.5	386.8	-2.8	-0.6	
SD	23.73	21.74	21.30	5.52	21.12	20.47	18.85	4.81	

1: Endpoint is the last valid record post-treatment.
2: P-value is based on the test for the difference of change from baseline to endpoint between the two treatment groups using one way ANCOVA with t
baseline as a covariate and treatment as main effect.
Source: Appendix 1, ISS Table 8.11.1

Table 24 Mean Change in ECG Parameters in Subjects in SLI381.304

	ADDERALL XR®			
Study 381.304	Baseline	Endpoint Actual[1]	Change	%Change
Original sNDA				
PR (msec)				
N	223	222	222	222
Mean	150.3	145.3	-5.0	-2.7
SD	21.15	17.87	14.66	9.48
QRS (msec)				
N	223	222	222	222
Mean	89.3	89.7	0.3	0.7
SD	6.84	6.32	6.86	7.67
QT (msec)				
N	223	222	222	222
Mean	370.0	362.5	-7.5	-1.8
SD	26.35	26.10	23.08	6.34
QTc (msec)				
N	223	222	222	222
Mean	395.9	398.7	2.5	0.6
SD	21.08	22.75	22.04	5.58
Current Update				
PR (msec)				
N	223	222	222	222
Mean	150.3	145.3	-5.0	-2.6
SD	21.15	17.56	14.82	9.56
QRS (msec)				
N	223	222	222	222
Mean	89.3	89.3	-0.1	0.2
SD	6.84	6.74	6.85	7.66
QT (msec)				
N	223	222	222	222
Mean	370.0	364.1	-5.9	-1.4
SD	26.35	27.40	25.17	6.85
QTc (msec)				
N	223	222	222	222
Mean	395.9	401.7	5.6	1.6
SD	21.08	22.12	22.51	5.74

[1]Endpoint is the last valid record post-treatment.

Source: ISS Table 8.11.1 of the original sNDA and the current update (Appendix 1)

28. Summary of Changes in Vital Signs (303, 304)

Table 21 Summary of Changes in Vital Signs: Controlled trial (SLI381.303)

Parameter	ADDERALL XR®				Placebo				
	Baseline	Endpoint[1]	Change	%Change	Baseline	Endpoint	Change	%Change	P-Value[2]
Systolic BP (mmHg)									
N	191	187	187	187	64	60	60	60	
Mean	119.0	120.9	1.9	2.0	118.1	116.5	-1.5	-1.4	0.0068
SD	11.61	12.19	11.38	9.84	11.08	12.23	10.12	8.62	
Diastolic BP (mmHg)									
N	191	187	187	187	64	60	60	60	
Mean	76.2	78.7	2.5	4.2	76.2	79.4	2.1	3.2	0.7308
SD	9.12	9.09	9.32	13.13	8.63	9.37	7.90	10.95	
Pulse (bpm)									
N	191	187	187	187	64	60	60	60	
Mean	71.3	76.6	5.2	8.2	71.2	73.0	1.9	3.5	0.0133
SD	8.81	10.64	10.65	15.69	8.05	9.23	10.42	15.22	
Weight (lb.)									
N	169	161	161	161	90	88	87	87	
Mean	183.1	177.6	-4.5	-2.5	185.2	185.3	0.2	0.1	<0.0001
SD	40.55	38.31	5.09	2.80	41.09	43.37	3.92	3.29	

[1] Endpoint is the last valid record post-treatment.

[2] P-value is based on the test for the difference of change from baseline to endpoint between the two treatment groups using one way ANCOVA with Baseline as covariate and treatment as main effect.

Source: Appendix 1, ISS Table 8.10.1

Table 22 Summary of Changes in Vital Signs: Uncontrolled trial (SLI381.304)

Parameter	Baseline	Endpoint[1]	Change	Percent Change
Original sNDA				
Systolic BP (mmHg)				
N	223	222	222	222
Mean	119.8	119.1	-0.7	-0.2
SD	12.27	12.35	10.92	9.17
Diastolic BP (mmHg)				
N	223	222	222	222
Mean	78.9	78.1	-0.8	-0.3
SD	9.10	9.17	9.28	12.03
Pulse (bpm)				
N	223	222	222	222
Mean	75.8	78.2	2.4	4.2
SD	10.46	11.40	12.06	16.12
Weight (lb.)				
N	222	43[2]	43	43
Mean	179.2	177.4	-3.1	-1.3
SD	40.81	37.18	12.61	5.78
Current Update				
Systolic BP (mmHg)				
N	223	222	222	222
Mean	119.8	121.0	1.2	1.4
SD	12.27	12.50	11.20	9.63
Diastolic BP (mmHg)				
N	223	222	222	222
Mean	78.9	79.0	0.2	1.0
SD	9.10	8.35	8.89	11.51
Pulse (bpm)				
N	223	222	222	222
Mean	75.8	79.5	3.6	6.1
SD	10.46	11.94	13.63	18.90
Weight (lb.)				
N	222	69[2]	69	69
Mean	179.2	178.0	-3.5	-1.6
SD	40.81	39.38	11.83	5.85

[1] Endpoint is the last valid record post treatment.
[2] Data for all subjects not yet available. Ongoing Study.
Source: ISS Table 8.10.1 of the original sNDA and the current update (Appendix 1)

29. AE's by Age Group

Table 26 Incidence of Selected Adverse Events by Age Group with ADDERALL XR® (SLI381.303 and SLI381.304)

BODY SYSTEM Preferred Term	39 Years and Younger N=132		40 Years and Older N=116	
	Number (%) of Subjects Reporting	Number of AEs	Number (%) of Subjects Reporting	Number of AEs
ANY ADVERSE EVENT	123 (93.2%)	892	112 (96.6%)	813
BODY AS A WHOLE	77 (58.3%)	170	65 (56.0%)	158
Headache	44 (33.3%)	64	37 (31.9%)	65
CARDIOVASCULAR	24 (18.2%)	35	19 (16.4%)	30
Hypertension	5 (3.8%)	6	2 (1.7%)	2
Palpitation	5 (3.8%)	8	8 (6.9%)	11
Tachycardia	9 (6.8%)	11	6 (5.2%)	8
DIGESTIVE	95 (72.0%)	255	79 (68.1%)	194
Anorexia	57 (43.2%)	84	41 (35.3%)	53
Constipation	8 (6.1%)	9	12 (10.3%)	15
Diarrhea	8 (6.1%)	8	9 (7.8%)	9
Dry mouth	60 (45.5%)	98	55 (47.4%)	81
Nausea	20 (15.2%)	24	14 (12.1%)	14
METABOLIC/NUTRITION	33 (25.0%)	39	17 (14.7%)	32
Weight loss	29 (22.0%)	34	8 (6.9%)	12
NERVOUS	86 (65.2%)	258	86 (74.1%)	267
Agitation	11 (8.3%)	17	17 (14.7%)	30
Anxiety	18 (13.6%)	24	14 (12.1%)	18
Insomnia	45 (34.1%)	67	47 (40.5%)	74
Nervousness	31 (23.5%)	50	25 (21.6%)	38

Source: Appendix 1, ISS Table 6.8.2 Part A

30. Laboratory Tests Statistically Significant Mean Changes (Study 303)

Table 8-34 Statistically Significant ($p < 0.05$) Mean Changes from Baseline to Endpoint in Laboratory Tests; Comparison to Placebo

Laboratory Parameter[1]		Placebo (N=64) Mean (SD)	ADDERALL XR® 20 mg (N=66) Mean (SD)	ADDERALL XR® 40 mg (N=64) Mean (SD)	ADDERALL XR® 60 mg (N=61) Mean (SD)
Eosinophils ($\times 10^3/\mu L$)	Baseline	0.10 (0.119)	0.19 (0.155)	0.10 (0.130)	0.18 (0.118)
	Endpoint	0.18 (0.105)	0.19 (0.144)	0.16 (0.120)	0.14 (0.086)
	Change[2]	-0.00 (0.103)	-0.00 (0.105)	-0.02 (0.088)	-0.05 (0.098)
Eosinophils (%)	Baseline	2.8 (1.52)	2.9 (1.93)	2.9 (1.92)	2.8 (1.67)
	Endpoint	2.9 (1.72)	3.0 (2.21)	2.5 (1.53)	2.1 (1.46)
	Change	0.1 (1.42)	0.0 (1.59)	-0.3 (1.38)	-0.6 (1.36)
Total Protein (g/dL)	Baseline	7.36 (0.420)	7.28 (0.378)	7.39 (0.475)	7.32 (0.367)
	Endpoint	7.31 (0.365)	7.23 (0.334)	7.43 (0.393)	7.33 (0.332)
	Change	-0.06 (0.331)	-0.03 (0.357)	0.05 (0.389)	0.03 (0.296)
GGT (IU/L)	Baseline	25.3 (19.83)	26.0 (14.26)	35.5 (39.74)	25.3 (19.67)
	Endpoint	25.8 (24.05)	22.7 (11.33)	28.1 (25.68)	20.4 (11.37)
	Change	0.2 (8.94)	-3.0 (5.10)	-7.0 (18.83)	-5.2 (11.29)
Cholesterol (mg/dL)	Baseline	200.3 (33.65)	204.4 (38.75)	203.8 (38.40)	204.8 (42.70)
	Endpoint	197.1 (35.82)	189.4 (36.82)	188.4 (38.32)	185.7 (38.62)
	Change	-2.4 (22.88)	-15.5 (25.63)	-16.0 (23.46)	-18.6 (28.62)
VLDL (mg/dL)	Baseline	32.5 (23.28)	33.8 (25.55)	27.5 (16.12)	35.2 (19.93)
	Endpoint	32.7 (19.81)	28.3 (21.01)	23.6 (13.03)	27.0 (16.33)
	Change	-0.4 (17.23)	-6.1 (15.26)	-4.0 (11.18)	-8.4 (15.52)
Triglycerides (mg/dL)	Baseline	162.0 (116.55)	169.4 (127.88)	137.4 (80.55)	176.2 (99.71)
	Endpoint	163.2 (99.04)	141.4 (105.18)	118.0 (65.20)	134.9 (81.86)
	Change	-1.8 (86.21)	-31.0 (75.95)	-20.0 (55.71)	-42.1 (77.99)

[1]Number of subjects varied from test to test due to missing data

[2]Change from baseline at endpoint

Source: Clinical Study Report SLI 381 303; Table 25

31. Non-Fatal Serious Adverse Events

Table 14 Serious Adverse Events

Subject ID	Age (yrs)	Sex	Dose[1] (mg)	Adverse Event	Duration of Treatment[2]	Relationship to Treatment	Action Taken	Outcome
SAEs reported in the original sNDA								
381.304/ 102-015	40	F	60 mg	Pneumococcal sepsis	9 weeks	Unrelated	ADDERALL XR® discontinued; treated with intravenous antibiotics.	Resolved
381.304/ 102-021	38	M	20 mg	Depression, suicidal ideation secondary to bipolar disorder	17 weeks	Related	ADDERALL XR® discontinued; treated with lorazepam, haloperidol, and olanzapine.	Resolved
381.304/ 108-005	44	F	60 mg	Cholecystitis	6 weeks	Unrelated	ADDERALL XR® temporarily withheld; Cholecystectomy	Resolved
SAEs reported after the submission of the original sNDA								
381.304/ 104-038	21	M	40 mg	Accidental injury (hands burn)	33 weeks	Unrelated	Hospitalization for about 2 weeks	NA
381.304/ 112-019	59	F	20 mg	Kidney calculus	28 weeks	Unrelated	Hospitalization; ADDERALL XR® temporarily discontinued;	Resolved
381.304/ 116-012	35	F	20 mg	Headache	15 weeks	Unrelated	Hospitalization; treated with analgesics; ADDERALL XR® discontinued;	Resolved

[1]Daily dose of ADDERALL XR® at the time of the event or last dose prior to the event.

[2]Total duration of treatment in Study SLI381.304

Source: Clinical Study Report SLI381.304, Table 12 and patient narratives and Appendix 1, ISS Table 8.7.3

E. Marketing Exclusivity Claim

Shire is claiming 3 year marketing exclusivity under 21 CFR 314.50 (j) and 21 CFR 314.108 (b)(5) for Adderall XR for the treatment of ADHD in adults and its related strengths. Shire states that the new clinical investigations which were conducted as defined by 21 CFR 314.108 (a) are:
SLI381.303, the 4 week, double bind, placebo controlled study and SLI381.304, the incomplete, 12 month, incomplete open label study.

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

/s/

Glenn Mannheim
10/1/03 02:43:05 PM
MEDICAL OFFICER

Paul Andreason
10/9/03 03:32:13 PM
MEDICAL OFFICER
Please see memo to file dated 9OCT2003.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

021303Orig1s005

CHEMISTRY REVIEW(S)

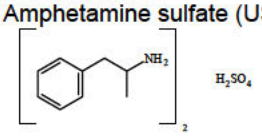
CHEMIST'S REVIEW OF SUPPLEMENT

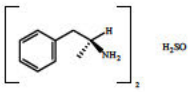
1. ORGANIZATION:	**HFD-120**
2. NDA NUMBER:	**21-303**
3. SUPPLEMENT NUMBER:	**SE5-005**
LETTER DATE	18-DEC-02
STAMP DATE	19-DEC-02
4. AMENDMENTS/REPORTS:	
LETTER DATE	N/A
STAMP DATE	N/A
5. RECEIVED BY CHEMIST:	29-JAN-03

6. APPLICANT NAME AND ADDRESS: Shire Laboratories Inc.
1801 Research Blvd, Suite 600
Rockville, MD 20850

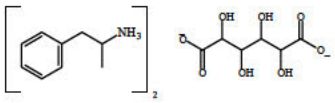
7. NAME OF DRUG: **ADDERALL XR®**

9. NONPROPRIETARY NAME: Amphetamine sulfate (USP), Dextroamphetamine sulfate (USP)

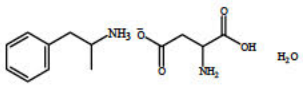




Dextroamphetamine saccharate



Amphetamine aspartate monohydrate



10. CHEMICAL NAME / STRUCTURE: Amphetamine sulfate (USP) [(±)-α-methylphenethylamine sulfate (2:1)]; dextroamphetamine sulfate (USP) [(+)-α-methylphenethylamine sulfate (2:1)]

11. DOSAGE FORM(S): Capsules

12. POTENCIES: 5 mg, 10 mg, 15 mg, 20 mg, 25 mg, 30 mg, (b) (4)

13. PHARMACOLOGICAL CATEGORY: ADHD/Narcolepsy

14. HOW DISPENSED: **XX (Rx) (OTC)**

15. RECORDS / REPORTS CURRENT: **XX (YES) (NO)**

16. RELATED IND / NDA / DMF(s): N/A

17. CONSULT: None

SUPPLEMENT PROVIDES FOR: 1) the treatment of ADHD in adults (b) (4)

COMMENTS: This supplement (b) (4) for the treatment of adults with ADHD. The original submission of NDA 21-303, submitted 03-OCT-00 and approved 11-OCT-01, described three finished drug product strengths, ADDERALL XR® capsules, 10 mg, 20 mg, and 30 mg. NDA 21-303 Supplement 001, dated 26-OCT-01 and approved 22-MAY-02, described three additional finished product strengths, ADDERALL XR® capsules, 5 mg, 15 mg, and 25 mg. (b) (4)

(b) (4)

CONCLUSIONS AND RECOMMENDATIONS: Based on the information provided, this supplement is recommended for **APPROVAL** from a CMC perspective.

REVIEWER NAME	SIGNATURE	DATE COMPLETED
Chhagan G. Tele, Ph.D.		August 15, 2003

cc: Orig.; NDA 21-303
HFD-120/Div. File
HFD-120/PM/AHomonnay
HFD-120/CTele
INIT: TOliver

Filename: s21-303.005

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/s/

Chhagan Tele
8/15/03 12:40:45 PM
CHEMIST

Thomas Oliver
8/15/03 01:20:27 PM
CHEMIST

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

021303Orig1s005

STATISTICAL REVIEW(S)

Statistical Review and Evaluation

NDA#:	**21303 S-005 ,** (b) (4)
Name of Drug:	**Adderall XR™**
Name of Firm:	**Shire Pharmaceutical Development, Inc.**
Indication:	**Adult ADD**
Date of Document:	**February 13, 2004**
Medical Officer:	**Teresa Podruchny, M.D. (HFD-120)**
Statistical Reviewer:	**Tristan Massie, Ph.D. (HFD-710)**

This is a review of Shire's response to FDA's Clinical Question 1 in the Approvable letter dated 17 October 2003. (b) (4)

[redacted]

FDA Clinical Question 1

Our review of Study 303 suggests that efficacy does not increase with doses greater than 20 mg/day. Though doses of 40 and 60 mg separated from placebo and were effective in the treatment of ADHD, and there appears to be a numerical increase in the estimate of the treatment effect with increasing dose, our analyses suggest that there is no linear dose trend. We acknowledge that there did not seem to be a response for reported adverse events in Study 303; however, we have been unable to find analyses of subjects who met outlier criteria for vital sign changes by dose. We ask you to provide these analyses. (b) (4)

(b) (4)

[redacted]

Design of Study 303

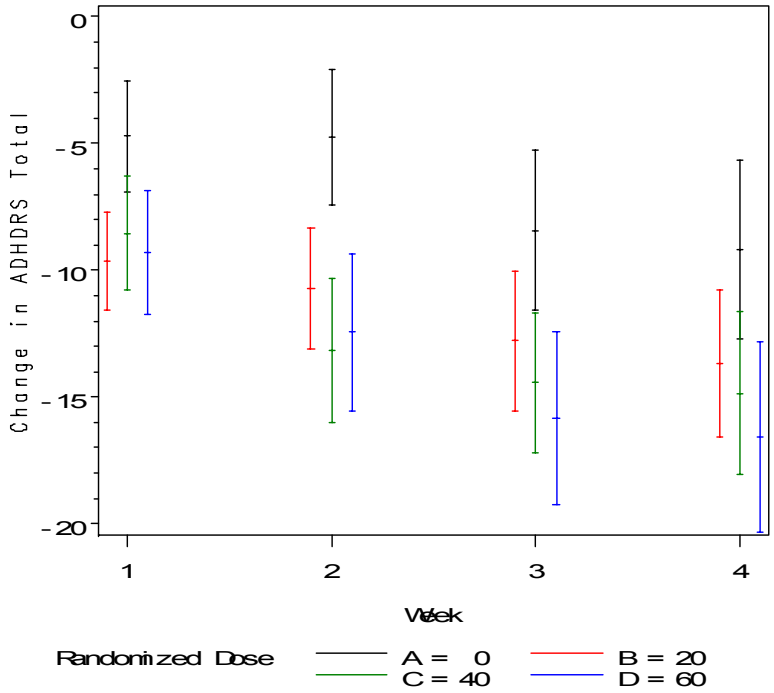
This trial was a randomized, double-blind, placebo-controlled, parallel-group design conducted in the U.S. Its primary objective was to examine the efficacy of 20, 40, and 60 mg Adderall XR compared to placebo in adult ADHD patients over 4 weeks of double-blind treatment. A total of 255 subjects were randomized at 18 centers with 64 in placebo, 66 in 20 mg Adderall XR, 64 in 40 mg Adderall XR, and 61 in the 60 mg Adderall XR group. The double-blind phase was 4 weeks with 1-2 weeks of forced titration (20 mg increase per week after the first week for 40 and 60 mg groups until target reached). The primary analysis was ANCOVA of the ADHD-RS Total score at the

end of week 4 for the ITT population (using LOCF) with Baseline Total score as the covariate and fixed effects for treatment groups and centers.

Results

Each dose was significantly different from placebo at endpoint based on the primary analysis. Figure 1 shows how the mean ADHD-RS scores changed over time for the randomized groups. The issue under question is whether or not the 40 and 60 mg doses provided more benefit than the 20 mg dose. This reviewer does not believe that the higher dose groups showed more benefit than the 20 mg dose. It is true that the least squares means are ordered as would be required for a linear trend, but the differences between them are small compared to the variability. The Least Squares Means based on the primary analysis of the change in ADHD-RS at endpoint using LOCF are –6.61, -7.17, and –7.78 with associated confidence intervals (-10.95,-2.27), (-11.52, -2.82), and (-12.19, -3.38) for Adderall XR 20, 40, and 60 respectively. Notice that each of the three confidence intervals contains all three LSmeans. This suggests that, despite the ordering of the LSmeans, the higher doses may not be more efficacious.

Figure 1 Change from Baseline in ADHD-RS Total Score By Week



The Adderall groups are displayed around a particular week in order of increasing dose from left to right so that the lines do not overlap.

It is true though that the study was not powered for comparisons between the Adderall groups. A test for linear trend is a more powerful option for assessing the added benefit

of the higher doses. The evidence for a linear trend among the original 20, 40, 60 groups (excluding placebo) is not very impressive (p=0.62) for the ITT population at endpoint using LOCF. The same is true for the Completers population (p=0.52). Nor did this reviewer find any significant pairwise comparisons between the 20, 40, and 60 mg (randomized) groups at any week based on either LOCF or Observed Case data (even without adjusting for multiple comparisons).

The sponsor made the case that there was insufficient power for comparisons between the different Adderall randomized groups and that because of the titration the assigned dose didn't necessarily represent the actual dose received. They presented numerous new analyses based on the actual dose groups and a post-hoc subgroup of patients with a baseline ADHD-RS Total score greater than the median, 32.

Sponsor's New Analyses based on Reassignment According to Actual Dose

The completion rates were relatively similar in the randomized groups: 70% for placebo, 73% for Adderall XR 20, 77% for Adderall XR 40, and 75% for Adderall XR 60. In the sponsor's new analyses they re-assigned those randomized to 60 mg (40 mg) who did not reach 60 mg (40 mg) to their actual dose. For example, a patient who was randomized to the 60 mg group and provided only 2 weeks of post-baseline ADHD-RS Total scores would be in the 20 mg group in week 1 and the 40 mg group for the remaining weeks and would have the week 2 observation carried forward for weeks 3 and 4. This means that at each week dropouts are reassigned to lower dose groups. This creates an imbalance between the groups in the average time of last observation with the average time smallest in the 20 mg actual dose group and largest in the 60 mg actual dose group. A test for a difference between completers and non-completers in mean ADHD-RS Total change scores is significant ($p<0.0001$). As seen in figure 1 above, scores tended to improve over time for all groups, even for the placebo and 20 mg Adderall groups for which there was no titration. Since ADHD-RS scores improved over time in all three original Adderall groups the reassignment and the associated time imbalance leads to a worse average score for the 20 mg final dose group and a better average score for the 60 mg final dose group, i.e., it artificially makes the data more supportive of a trend among the doses. This can be seen in Table 1 and Figure 2. Figure 2 shows that the reassignment to actual dose for patients randomly assigned to 40 mg and 60 mg, who did not reach their assigned dose, reduces the improvement seen in the randomly assigned 20 mg and 40 groups. Note that the sponsor appears to have placed 2 patients randomized to 40 mg and 2 patients randomized to 60 mg in the 40 mg actual dose group at endpoint although they had no efficacy data after week 1. However, this did not appear to affect the results. The average times of last observation at endpoint for the 20, 40, and 60 actual dose groups are 3.20 +/- 0.14 S.E., 3.46 +/- 0.12 S.E., and 3.94 +/- 0.03 S.E., respectively. Because of the time imbalance it is not possible to attribute the differences between the actual dose groups solely to the difference in the doses. There may also be imbalances between the actual dose groups in other characteristics as well since the patients are not reassigned randomly.

For each week the sponsor used a 1-way ANCOVA model for the ADHD-RS Total using LOCF with the actual dose as the effect and the baseline ADHD-RS Total as covariate.

The sponsor highlighted an LS Mean difference of -3.8 and a p-value of 0.0482 between the 60 mg (N=49) and 20 mg (N=71) actual dose groups at the end of week 3 and an LS Mean difference of -3.4 and a p-value of 0.0902 between the 60 mg and 20 mg actual dose groups at the end of week 4. Also presented were insignificant (all p>0.15) differences between the 20 mg and 40 mg actual dose groups at the end of week 2 and 20 and 40 mg and 40 and 60 mg actual dose groups at the ends of weeks 3 and 4.

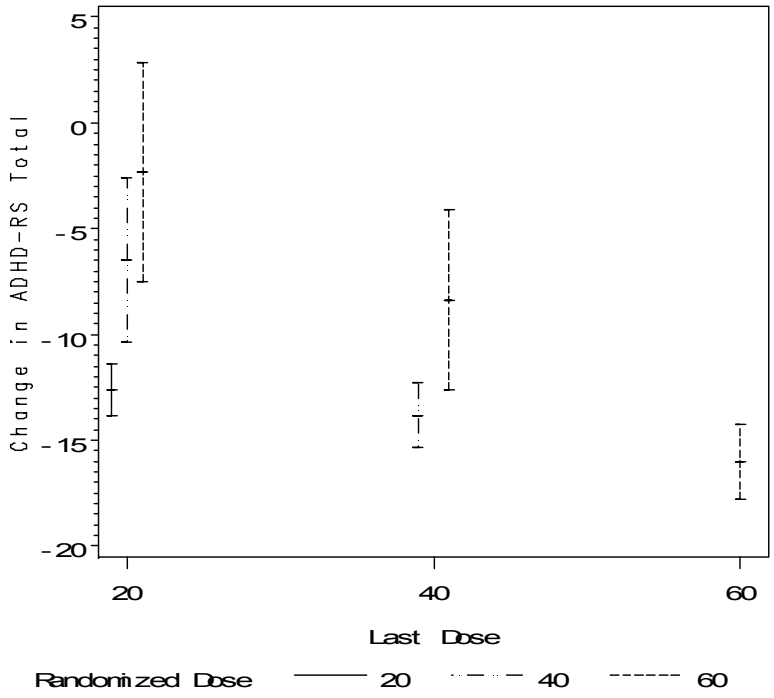
Three major problems with these new analyses by the sponsor are:

- The reassignment is problematic because it is not at random and therefore may create imbalances between the groups in variables associated with the Change in ADHD-RS.
- The comparisons between the actual dose groups which use LOCF are testing a mixture of the difference in doses and the time effect (improvement over time).
- The sponsor's closed testing procedure controlled the type I error for comparing multiple groups at a single time but not at multiple times.

Table 1 Change in ADHD-RS Total (LOCF) after each Week

		Randomly Assigned Treatment Group (Placebo Not Shown)											
		B = 20			**C = 40**			**D = 60**			**All**		
Week	**Actual Dose**	N	Mean	StdErr	N	Mean	StdErr	N	Mean	StdErr	N	Mean	StdErr
1	20	64	-9.6	1.0	64	-8.5	1.1	60	-9.3	1.2	188	-9.2	0.6
2	20	64	-11.0	1.1	6	-5.2	4.4	1	-3.0	.	71	-10.4	1.1
	40	.	.	.	58	-13.1	1.4	59	-12.1	1.5	117	-12.6	1.0
3	20	64	-12.0	1.2	6	-5.2	4.4	1	-3.0	.	71	-11.3	1.2
	40	.	.	.	58	-13.6	1.3	10	-7.1	3.7	68	-12.6	1.3
	60	.	.	.	.	.	.	49	-15.8	1.7	49	-15.8	1.7
4	20	64	-12.6	1.3	6	-5.2	4.4	1	-3.0	.	71	-11.9	1.2
	40	.	.	.	58	-13.7	1.5	10	-7.1	3.7	68	-12.7	1.4
	60	.	.	.	.	.	.	49	-16.0	1.8	49	-16.0	1.8

Figure 2 Effect of Reassignment on Group Mean Changes in ADHD-RS (LOCF) at Endpoint



Note that the last dose values were modified slightly for the graph so that the lines would not overlap.

Subgroup Analysis

The sponsor presented similar comparisons between the actual dose groups for each week in the subgroup of patients with baseline ADHD-RS Total scores >=32 (the median). But an analysis of this subgroup was not pre-specified, so the significance level should be lower than 0.05, since other subgroups may have been investigated as well, and the results should be considered exploratory.

They reported that the 60 mg actual dose group was better than the 20 mg actual dose group at the ends of weeks 3 and 4 (p=0.0083 and p=0.0010, respectively) and the 60 mg was also better than the 40 mg actual dose group at the ends of weeks 3 and 4 (p=0.0249 and p=0.0945, respectively). However, in the alternate subgroup, those with baseline ADHD-RS < 32, for all pairwise comparisons between Adderall actual dose groups the lower actual dose group was always numerically better than the higher actual dose group, except for the 20 mg vs. 40 mg actual dose group comparison at week 3.

The sponsor's subgroup analyses of the actual dose groups also used LOCF and therefore they are testing a mixture of the difference in doses and the time effect. This reviewer

found that based on the original randomization a test for a linear trend among the doses in the Baseline ADHD-RS Total >=32 subgroup at endpoint using LOCF yielded a p-value of 0.06. However, for the Baseline < 32 group the test for a linear trend had a p-value of 0.07 with the trend in the opposite direction, i.e., the 20 group was numerically better than the 40 and 60 groups. This is a frequent problem with findings in unplanned subgroups. When the overall result is not positive but the subgroup is positive the complimentary subgroup may go in the opposite direction and make the result in the positive subgroup less credible. Such subgroups are often found when one conducts many tests, so independent confirmation is needed.

Incremental Change from Week to Week

The sponsor also analyzed the incremental change from the preceding week for each week using the actual dose received groups and LOCF. This data also has a time imbalance between the groups which favors the higher dose. For example, after the second week patients randomized to 60 mg increased their dose from 40 mg to 60 mg while patients randomized to 40 mg continued taking 40 mg. There were 3 patients randomized to 40 mg and 8 patients randomized to 60 mg whose last assessment was at the end of week 2 so their last dose was 40 mg. They are included in the analysis using LOCF so they have no change from week 2. This biases the incremental change towards 0 for the 40 mg group and thus artificially makes the 60 mg group look better.

The sponsor presented a significant difference in incremental change between the actual 40 and 60 mg groups for the ITT population at the end of week 3 (p=0.0351). But if we omit the individuals who had no week 3 score the result is no longer significant (p=0.1972). Furthermore, since the difference in incremental change from week 3 to week 4 is in the opposite direction, i.e., favors the 40 mg over the 60 mg group (although not significant), the incremental change did not consistently favor 60 mg over 40 mg and therefore the week 2 to week 3 difference observed is less compelling.

In addition, except for the 60 mg vs. 40 mg comparison at the end of week 3 in the subgroup with baseline ADHD-RS Total >=32 the p-values are considerably larger for the more appropriate though less powerful Observed Cases analysis of Incremental change by week. Note also that the sponsor's analyses suggest that the incremental change from week 3 to 4 for the 40 mg group was significantly worse than the 20 mg group p=0.0247 in the subgroup with baseline ADHD-RS Total < 32. (b) (4)

[redacted]

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Proportions improved on CGI-I for Actual Dose Groups

Finally, the sponsor presented the group proportions classified as either much improved or very much improved on the CGI-I for the actual dose groups. They reported significant Mantel Haenszel tests for nonzero correlation between proportion and dose for weeks 2, 3, and 4 (p=0.0299, 0.0115, and 0.0410, respectively). However, the same test was not significant for the ITT-LOCF or Observed Cases analyses of the randomized groups at the end of week 4 (p=0.3500 and 0.3245, respectively). As for the ADHD-RS, the

differences between the results for the randomized groups and the actual dose groups can be explained by the fact that the CGI-I scores tended to improve over time (see Table 2) and the reassignment according to actual dose creates a time imbalance between the groups which artificially makes the 60 mg dose look better.

Table 2 Proportion with CGI-I <= 2 by Week for Randomized Groups

Week		PLACEBO	20	40	60
1	%Improved	16.7	29.7	23.5	31.6
	N Total	60	64	64	60
2	%Improved	19.7	34.5	51.8	50.9
	N Total	56	58	56	57
3	%Improved	28.9	49.0	60.4	67.4
	N Total	45	51	53	49
4	%Improved	35.7	55.3	66.0	65.3
	N Total	42	47	50	46
End-LOCF	%Improved	26.7	50.0	56.3	58.3
	N Total	60	64	64	60

Conclusion

The sponsor has submitted new analyses designed to show that the higher Adderall XR doses were more efficacious than Adderall XR 20 mg. One such analysis reassigns patients who did not achieve their randomly assigned dose to the dose group corresponding to the last dose they achieved. The sponsor found some differences favoring higher over lower actual doses in the ITT population using LOCF based on this approach. However, these new groups are no longer balanced with respect to time of last observation and since all the randomized groups exhibited improvement over time the reassignment artificially makes the 20 mg dose look worse and the 60 mg dose look better. The reassignment to actual dose is also problematic because it is not at random and therefore may create imbalances between the groups in other variables associated with the Change in ADHD-RS. Also, the sponsor's closed testing procedure did not adjust for repeating the group comparisons at each week.

The sponsor also found some differences favoring the 60 mg group over the 20 and 40 mg actual dose groups in the subgroup of patients with a baseline ADHD-RS Total score >= 32 (the median), but this subgroup was not prespecified in the protocol and in the baseline ADHD-RS Total score < 32 subgroup the trend was in the opposite direction. This is a frequent problem with findings in unplanned subgroups. When the overall result is not positive but the subgroup appears to be positive the complimentary subgroup may go in the opposite direction and make the result in the "positive" subgroup less credible. Such subgroups are often found when one conducts many tests, so independent confirmation is needed.

The evidence for a linear trend among the original 20, 40, 60 randomized groups (excluding placebo) is not impressive (p=0.62) for the ITT population at endpoint using LOCF. The same is true for the Completers population (p=0.52). While the two week

titration period may have made it difficult to show a dose-response it also reduced the exposure to the high dose and therefore the chance of observing adverse events at the high dose. In conclusion, although the study was not powered to compare the different Adderall XR doses the evidence that additional benefit is gained from a higher dose is not convincing.

cc:
HFD-120/Dr. Katz
HFD-120/Dr. Andreason
HFD-120/Dr. Podruchny
HFD-120/Ms. Taylor
HFD-700/Dr. Anello
HFD-710/Dr. Mahjoob
HFD-710/Dr. Hung
HFD-710/Dr. Jin
HFD-710/Dr. Massie
This review consists of 8 pages.

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

/s/

Tristan Massie
7/16/04 02:22:50 PM
BIOMETRICS

Sharon Yan
7/16/04 02:29:17 PM
BIOMETRICS

James Hung
7/16/04 05:24:22 PM
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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF PHARMACOEPIDEMIOLOGY AND STATISTICAL SCIENCE
OFFICE OF BIOSTATISTICS

STATISTICAL REVIEW AND EVALUATION

Clinical Studies

NDA/Serial Number:	21-303 (SN: 005)
Drug Name:	Adderall XR
Indication:	Adult ADHD
Sponsor:	Shire Pharmaceuticals
Date:	12/18/2002
Review Priority:	Standard
Biometrics Division:	Biometrics I (HFD 710)
Statistical Reviewer:	Tristan Massie
Concurring Reviewers:	Kun Jin, Ph.D.,Team Leader George Chi, Ph.D., Director
Medical Division:	Neuropharmacological Drug Products (HFD 120)
Clinical Team:	Glenn Mannheim, M.D., Clinical Reviewer Paul Andreason, M.D., Team Leader Russell Katz, M.D., Director
Project Manager:	Anna Homonnay Weikel, R. Ph.

Keywords: ANCOVA, ADHD, Adderall XR

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Statistical Review and Evaluation

1. Executive Summary

1.1. Conclusions and Recommendations

The data and analysis from this single randomized, double-blind, parallel-group design study support the efficacy of Adderall XR in adults.

1.2. Brief Overview of Clinical Studies

This trial was a randomized, double-blind, placebo-controlled, parallel-group design conducted in the U.S. Its primary objective was to examine the efficacy of 20, 40, and 60 mg Adderall XR compared to placebo in adult ADHD patients over 4 weeks of double-blind treatment. A total of 255 subjects were enrolled at 18 centers with 64 in placebo, 66 in 20 mg Adderall XR, 64 in 40 mg Adderall XR, and 61 in the 60 mg Adderall XR group. The double-blind phase was 4 weeks with 1-2 weeks titration (20 mg increase per week for 40 and 60 mg groups until target reached). The primary analysis was ANCOVA of the ADHD-RS Total score at 4 weeks using LOCF with Baseline Total score as the covariate and fixed effects for treatment groups and centers.

1.3. Statistical Issues and Findings

The primary analysis of this single 4 week randomized trial shows that Adderall XR 20 mg, 40 mg, and 60 mg groups were significantly better than placebo at endpoint based on the ADHD-RS Total score. Although in the Study Completers population the Adderall XR 20 mg/Placebo comparison was not quite significant at the 0.05 level (p=0.058), placebo completers seem to have done better than placebo dropouts so this analysis may be biased against the Adderall XR 20 mg group.

The CAARS:S-S ADHD index, a secondary endpoint, was to be assessed at 4 hours and 12 hours post-dose on Mondays, Wednesdays, and Fridays in an attempt to assess the duration of action. Although they are suggestive, the results of the CAARS:S-S analysis are not as clear cut as the primary analysis results for several reasons. First, many of the calls were not made close to the designated times and no time windows were specified in the protocol. Second, 21 ITT patients had insufficient data to be included in this analysis and it is not clear what effect they might have had on the analysis. Finally, although the treatment groups were superior to placebo at endpoint using the ITT population with the LOCF method, only the 60 mg group was found to be significant at 4 or 12 hours post-dose for the Observed Cases population.

2. Introduction

2.1. Overview

Adderall was previously demonstrated to be effective in treating symptoms of ADHD in children. Despite its effectiveness its use can be problematic because it must be taken several times during the day. Adderall XR is an extended release, single-entity, amphetamine product that was approved for use in children aged 6 to 12 in 2001. The study described herein was designed to show efficacy and safety of Adderall XR in adults with ADHD.

2.2. Data Sources

The data can be found at the following network location:
\\CDSESUB1\N21303\S_005\2002-12-18

3. Statistical Evaluation

3.1. Evaluation of Efficacy

3.1.1. Objectives of Study 381.303

The primary objective was to assess the efficacy and safety of ADDERALL XR™ (administered as a daily dose of 20, 40, or 60 mg) compared to placebo in the treatment of ADHD in adults.

The secondary objective was to assess the duration of action of ADDERALL XR™ using two time periods: 4 hours post-dose and 12 hours post-dose, three days a week, for the four weeks of treatment.

3.1.2. Study Design

This was a multi-center, randomized, double blind, parallel-group, placebo-controlled study of up to 6 weeks duration assessing the efficacy and safety of three fixed doses of ADDERALL XR™ compared to placebo in adults with ADHD. Approximately 200 subjects were to be randomized.

Eligible subjects were male or female 18 years of age or older who satisfied DSM-IV-TR criteria for a primary diagnosis of ADHD. There were also other inclusion criteria such as IQ > 80 and no comborbid psychiatric diagnosis.

Following a 1 week washout of previous stimulant treatment (if any), subjects meeting entry

criteria were randomly assigned in a 3:1 ratio (active: placebo) to a once daily morning dose for 4 weeks. Six visits were scheduled: one or more to screen candidate subjects (Visit 1-Screening), one to dispense double-blind study medication and perform baseline assessments (Visit 2 –Baseline), and four weekly visits to assess double-blind treatment effects (Visits 3, 4, 5, and 6). Subjects receiving active drug were randomized to one of three treatment groups: 20 mg/day, 40 mg/day, or 60 mg/day. Subjects randomized to 20 mg/day started and continued at that dose for four weeks. Subjects randomized to 40 mg/day were titrated to that dose over a 1-week period (20 mg/day for the first week, then 40 mg /day) and continued at that dose for 3 weeks. Subjects randomized to 60 mg/day were titrated to that dose over a 2-week period (20 mg/day for the first week, 40 mg for the second, and 60 for the final two weeks). This was a forced dose titration experimental design, and dosage modification based upon efficacy evaluations or impressions was not permitted. Visits were scheduled 7 days apart (± 2 days), with a minimum of 5 days between visits. If a visit was not completed on the scheduled day of assessment, the next visit was completed per the original schedule.

3.1.3. Efficacy Measures

The ADHD-RS score for adults is obtained by summing the answers (each of which is coded from 0 (no symptoms) to 3(severe symptoms)) to 18 questions related to hyperactivity/impulsivity or inattentiveness. The score ranges from 0 to 54 with 0 being perfectly normal. This measure is assessed by the patient with the physician at visits 3, 4, 5, and 6, and is based on ADHD symptoms during the week prior. The primary efficacy endpoint was defined as the last post-baseline visit for which a valid ADHD-RS score was obtained. This was numerically equivalent to the method of last observation carried forward.

Secondary endpoints will include Conner's Adult ADHD Rating Scale Self-Report: Short Version (CAARS-S:S), Clinical Global Impressions Scale (CGI), Hamilton Depression Rating Scale (HAM-D), Hamilton Anxiety Rating Scale (HAM-A), Social Adjustment Scale-Self Report (SAS-SR), and Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q). Duration of action will be assessed through the use of the Conners' Adult ADHD Rating Scale (CAARS-S:S), using an interactive voice response system. During the 7-day washout period, subjects should complete the CAARS-S:S at both lunch and dinner time on three separate days (Monday, Wednesday, and Friday). During each of the four treatment weeks, subjects should complete the self-report scale at 4 hours post-dose and 12 hours post-dose, on three days (Monday, Wednesday, and Friday).

3.1.4. Statistical Analysis Plan

The primary efficacy analysis will be carried out using the ITT population. It will consist of a two-

way analysis of covariance using the ADHD-RS Total score from a subject's final treatment week as the dependent variable, the corresponding baseline score as a covariate, and the treatment and study center as the independent variables. Based on the ANCOVA results, Dunnett's test for multiple mean comparisons, which controls the family-wise error rate at a pre-defined level, will be employed to compare each of the three active treatment groups and the placebo group. The type I error rate for rejecting a null hypothesis will be set at 0.05 for both the ANCOVA and Dunnett's test.

The CAARS-S:S primary subscale, ADHD index, a secondary endpoint, will be analyzed at endpoint (or LOCF) using an ANCOVA model with treatment and center as fixed effects and the baseline average of the ADHD index as a covariate. Type III sums of squares will be used to test for a treatment effect. If the hypothesis of no treatment effect is rejected then pairwise comparisons between the least squares means of each dose and placebo will be performed using a closed testing procedure: a t-test between the least squares means of Adderall XR 60mg and placebo will first be performed. If a significant difference is detected, the same test will be performed for Adderall XR 40 mg and placebo. Finally, if a significant difference is found for Adderall XR 40 mg then the same test will be performed for Adderall XR 20 mg and placebo. The CAARS-S:S is taken at both 4 and 12 hours post-dose on Monday, Wednesday, and Friday of each week. Duration of effectiveness will be assessed by individually analyzing the weekly averages of both the 4 hour and 12 hour ADHD subscales of the CAARS-S:S. If three or more of the 12 items which comprise the ADHD index subscale of the CAARS-S:S are missing, then it will be set to missing. Otherwise, missing items will be replaced with the mean of the non-missing items.

3.1.5. Study Population

Two hundred and fifty-nine subjects were enrolled in the study and entered the washout phase. Of these subjects, 4 were terminated prior to randomization, 3 had protocol violations (106-010, 126-011, 129-004), and one subject (108-008) was randomized in error. This latter subject was found to have high blood pressure at baseline. Two hundred and fifty five subjects were randomized. This number is larger than the 200 originally planned because enrollment exceeded expectations towards the end of the study.

Sixty-four subjects were randomized to placebo while sixty-six, sixty-four, and sixty-one were randomized to 20 mg, 40 mg, and 60 mg respectively. The numbers and percentages of completers in each group were 42 (65.6%), 47 (71.2%), 49 (76.6%), and 45 (73.8%) respectively. Lack of efficacy was the most frequent reason for withdrawal in the placebo group (21.9%) versus (6.6%-9.4%) for the Adderall groups. Adverse events were the most frequent reason for termination in the Adderall groups (9.4%-13.6%) versus (1.6%) placebo.

Table 3.1 Subject Disposition

	Placebo	Adderall XR 20 mg	Adderall XR 40 mg	Adderall XR 20 mg	Total
Randomized	64	66	64	61	255
Completed	42 (65.6)	47 (71.2)	49 (76.6)	45 (73.8)	183 (71.8)
Primary Reason for discontinuation n (%)					
Adverse Event	1 (1.6)	9 (13.6)	6 (9.4)	8 (13.1)	24 (9.4)
Protocol Violation	1 (1.6)	1 (1.5)	1 (1.6)	0 (0.0)	3 (1.2)
Withdrew consent	4 (6.3)	0 (0.0)	1 (1.6)	1 (1.6)	6 (2.4)
Lost to follow-up	2 (3.1)	4 (6.1)	1 (1.6)	3 (4.9)	10 (3.9)
Lack of Efficacy	14 (21.9)	5 (7.6)	6 (9.4)	4 (6.6)	29 (11.4)

Of the 255 randomized subjects, 32 had at least one major protocol deviation, which excluded them from the Per Protocol (PP) population. Twenty-three subjects were considered non-compliant, ten subjects violated inclusion/exclusion criteria, and 3 subjects were terminated prior to randomization due to violation of inclusion/exclusion criteria. Some subjects had more than one protocol violation.

Among the 248 subjects of the ITT population the average age was 39.2 (±11.4) years, with a range of 18 to 76, and the average weight was 183.5 (±41.0) lbs. Sixty percent of the subjects were male and 89% were white. Demographic and Baseline Characteristics for sex, race, age, weight, and height, as well as most recent prior ADHD treatment and baseline ADHD-RS Total Score are summarized by treatment group in the following table. For the most part these demographic characteristics were comparable among the four treatment groups. However, notice that the difference in the proportion of females between each dose and placebo increases as the dose increases. The proportion of females in the 60 mg group is in fact significantly different from the proportion in the placebo group.

The average length of time since ADHD diagnosis was 5.4 (±8.30) years. The average years since diagnosis for the 60 mg group was more than 2 years longer than any of the other groups. The median length of time since diagnosis for all subjects was 1 year in all groups with a range of 0 to 45 years.

Table 3.2 Demographic and Baseline Characteristics

		Placebo	Adderall XR 20 mg	Adderall XR 40 mg	Adderall XR 60 mg	Total
Age	Mean (SD)	39.3 (11.5)	38.8 (11.3)	38.9 (11.2)	39.9 (11.8)	39.2 (11.4)
Gender	Male	41 (68.3)	41 (64.1)	38 (59.4)	29 (48.3)	149 (60.1)
Gender	Female	19 (31.7)	23 (35.9)	26 (40.6)	31 (51.7)	99 (39.9)
Race	White	54 (90)	56 (87.5)	58 (90.6)	53 (88.3)	221 (89.1)
Race	Black	3 (5)	3 (4.7)	2 (3.1)	.	8 (3.2)
Race	Hispanic	2 (3.3)	4 (6.3)	2 (3.1)	5 (8.3)	13 (5.2)
Race	Asian	.	1 (1.6)	1 (1.6)	1 (1.7)	3 (1.2)
Race	Nat. Am.	.	.	1 (1.6)	1 (1.7)	2 (0.8)
Race	Other	1 (1.7)	.	.	.	1 (0.4)
Weight	Mean (SD)	185.9 (42)	181.1 (34)	185.4 (50)	181.6 (37)	183.5 (41)
Height	Mean (SD)	68.4 (4.42)	67.9 (3.71)	67.7 (3.87)	66.7 (3.71)	67.7 (3.96)
Years since Diagnosis	Mean (SD)	5.0 (7.24)	4.6 (6.79)	4.9 (8.57)	7.1 (10.22)	5.4 (8.30)
Predrug	unlisted	43 (71.7)	45 (70.3)	43 (67.2)	44 (73.3)	175 (70.6)
Predrug	antidepress	2 (3.3)	.	.	.	2 (0.8)
Predrug	bupropion	2 (3.3)	1 (1.6)	.	.	3 (1.2)
Predrug	citalopram	.	.	2 (3.1)	.	2 (0.8)
Predrug	dexamphet	2 (3.3)	.	.	2 (3.3)	4 (1.6)
Predrug	fluoxetine	1 (1.7)	.	.	.	1 (0.4)
Predrug	methy	.	1 (1.6)	1 (1.6)	.	2 (0.8)
Predrug	methy hcl	1 (1.7)	5 (7.8)	11 (17.2)	7 (11.7)	24 (9.7)
Predrug	obetrol	5 (8.3)	9 (14.1)	5 (7.8)	6 (10)	25 (10.1)
Predrug	venlafaxine	1 (1.7)	.	.	.	1 (0.4)
Predrug	all other	3 (5)	3 (4.7)	2 (3.1)	1 (1.7)	9 (3.6)
Baseline ADHD-RS Total	Mean(SD)	33 (8.7)	31.1 (9.6)	31.3 (8.1)	32.9 (9.8)	32 (9.1)

3.1.6. Sponsor's Efficacy Results

3.1.6.1. Primary Analysis

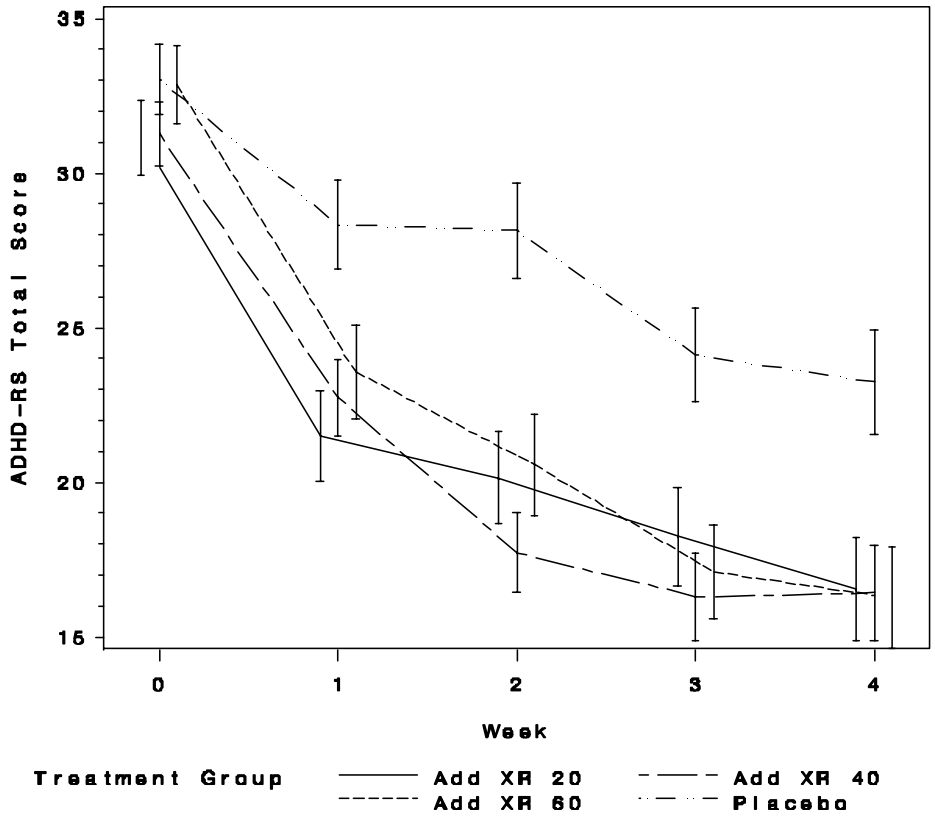
The primary efficacy endpoint was defined as the last post-baseline visit for which a valid ADHD-RS score was obtained. The primary efficacy analysis was the analysis of the ADHD-RS total score at endpoint for the ITT population. This consisted of an analysis of covariance (ANCOVA) model with baseline ADHD-RS total score as the covariate and treatment and center effects. Since each of the three dose groups was compared to placebo Dunnett's test was used to ensure proper control of the type I error. Using this approach, it was concluded that each of the dose groups were significantly more improved than placebo ($p=0.001$, $p<0.001$ and $p<0.001$ for Adderall XR™ 20, 40, and 60 mg respectively). The ANCOVA model based estimates of the differences in improvement are –6.61, -7.17, and –7.78 for Adderall XR™ 20, 40, and 60 mg respectively.

Table 3.3 ADHD-RS Total Score at Baseline and Endpoint for the ITT Population

		Placebo	Add XR 20	Add XR 40	Add XR 60
Baseline	N	60	64	64	60
	Mean (SD)	33.0 (8.75)	31.1 (9.61)	31.3 (8.13)	32.9 (9.83)
Endpoint	N	60	64	64	60
	Mean (SD)	26.4 (12.24)	18.5 (12.48)	18.4 (11.50)	18.5 (11.68)
	p value	N/A	0.001	<0.001	<0.001
Placebo-adjusted difference	LS Mean (95 % CI)	N/A	-6.61 (-10.95, -2.27)	-7.17 (-11.52, -2.82)	-7.78 (-12.19,-3.38)

The figure below shows the mean ADHD-RS Total score by week for each treatment group. All three groups were significantly more improved than placebo after the first week, during which all three groups received 20 mg. While the 40 and 60 mg groups were better than placebo for all subsequent visits, the 20 mg group was not significantly better than placebo for visit 5 or 6 ($p=0.065$ and $p=0.058$ respectively). Since only 65% of the placebo group and 72 % of the 20 mg group completed the study this latter finding may be due to the loss of power associated with dropouts.

Figure 3.1 Mean ADHD-RS Total Score by Week



Results for Per-Protocol and Study Completers Populations

The per-protocol population consisted of those subjects who received treatment for two weeks or more and did not have any major protocol deviations (206, 79.5%). Results for the per-protocol population were similar to those of the ITT population. Dunnett's test yielded statistically significant differences between each Adderall group and placebo ($p<0.001$, $p<0.001$, and $p<0.001$).

The study completers population consisted of those ITT subjects for whom the investigator indicated normal study completion (183, 70.7%). Dunnett's test yielded statistically significant differences between Adderall 40 mg and placebo (p=0.019) and Adderall 60 mg and placebo (p=0.013) but not between Adderall 20 mg and placebo (p=0.058). This may be an indication that the minimum effective dose is 20 mg.

3.1.6.2. Secondary Analyses

CAARS:S-S ADHD Index

The CAARS:S-S was to be completed two times post-dose, on Mondays, Wednesdays, and Fridays, so that duration of action could be assessed. The protocol stated that patients should call and take the CAARS:S-S (using an interactive voice response system) at 4 hours post dose and at 12 hours post dose on Mondays, Wednesdays, and Fridays. The protocol did not specify how close the calls had to be to 4 hours (or 12 hours) to be protocol compliant. The sponsor states in the report that: *"Of all individual calls, approximately 23% were made at 4 hours ± 30 minutes post-dose and about 15% were made at 12 hours ± 30 minutes post-dose. In order to maximize the use of the information available, therefore, two separate windows were applied to capture the data around each time point: 1-8 hours post-dose and 2-6 hours post-dose for the 4 hours post-dose analysis, and 9-16 hours post-dose and 10-14 hours post-dose for the 12 hours post-dose analysis".* An average of all CAARS:S-S ADHD subscale scores collected on Monday, Wednesday, and Friday was to be calculated separately for 4 hours post-dose and 12 hours post-dose for each double blind treatment week. Separate analyses of covariance of the 4 hour and 12 hour averages for the last week (or last observation carried forward) were used to compare the treatment groups. These ANCOVA models included effects for treatments, centers and the baseline average CAARS:S-S ADHD subscale. For both the 4 hour and the 12 hour analyses the baseline CAARS:S-S ADHD subscales was the average over all lunchtime and dinnertime CAARS:S-S ADHD subscales taken at baseline rather than just the lunchtime average or the dinnertime average. The ADHD subscale of the CAARS:S-S consists of 12 items each of which is scored from 0 to 3. Thus, the ADHD subscale ranges from 0 to 36 and higher scores are associated with more symptoms.

A closed testing procedure was to be applied separately to the 4 hour and 12 hour data to adjust for multiplicity issues associated with comparing multiple doses. First, the 60 mg dose would be compared to placebo and if this was not significant at the 0.05 level then testing would stop. If it was significant then the 40 mg dose would be compared to placebo. If the 40 mg dose was not significantly better than placebo at the 0.05 level then the 20 mg dose would not be compared to placebo. On the other hand, if the 40 mg dose was significantly better than placebo, then the 20 mg dose would be compared to placebo. Thus, the tests were to be performed in order and if a test was not significant then the remaining tests would not be carried out. As shown in the following table, for each time window all doses were found to be significantly better than placebo for the ITT population at endpoint, using LOCF.

Table 3.4 CAARS:S-S ADHD Index at endpoint for the ITT Population (LOCF)

Time Category: Hrs since last dose		Placebo	Add XR 20	Add XR 40	Add XR 60
Baseline	N *	54	60	59	54
	Mean (SD)	22.4 (5.7)	21.6 (5.8)	20.2 (5.4)	22.6 (5.4)
01-16 hrs	N *	54	59	58	54
	Mean (SD)	19.1 (7.0)	14.9 (7.1)	14.6 (6.8)	14.4 (6.8)
	p value #	N/A	0.002	0.012	<0.001
04hrs: 01-08	N *	54	57	56	54
	Mean (SD)	18.9 (7.0)	14.8 (7.3)	14.5 (6.9)	14.5 (6.9)
	p value #	N/A	0.003	0.017	<0.001
04hrs: 02-06	N *	54	57	56	53
	Mean (SD)	18.9 (7.0)	14.9 (7.3)	14.7 (6.9)	14.7 (6.9)
	p value #	N/A	0.004	0.021	<0.001
12hrs: 09-16	N *	52	57	55	54
	Mean (SD)	19.1 (7.0)	15.1 (7.3)	14.3 (6.8)	14.7 (6.8)
	p value #	N/A	0.003	0.006	<0.001
12hrs: 10-14	N *	52	56	55	53
	Mean (SD)	19.2 (6.9)	15.3 (7.3)	14.3 (6.8)	14.5 (6.6)
	p value #	N/A	0.004	0.006	<0.001

for comparison with placebo based on ANCOVA model with baseline score, treatment, and center effects
* Actual number of patients included in ANCOVA (sponsor reported number with non-missing endpoint which is sometimes larger)

ADHD-RS Subscales

The primary endpoint, ADHD-RS total score, is made up of the scores of two subscales: Hyperactivity/Impulsivity and Inattentiveness. All groups showed improvement over time on these scales. For each subscale all dose groups were found statistically better than placebo at endpoint using an ANCOVA model and Dunnett's test to adjust for multiple comparisons. There was little observable dose-response effect. However, Hyperactivity/Impulsivity scores increased slightly with increasing dose, while Inattentiveness scores decreased slightly with increasing dose.

Clinical Global Impressions

At baseline the severity of illness was evaluated using the CGI Severity Index (CGI-S), determined on a 7 point scale. At subsequent visits the subject's improvement relative to baseline was evaluated using the CGI Change (CGI-C) Index, also a 7-point scale. The protocol specified analysis of the CGI-C was based on the proportion of subjects who were classified as either "much improved" or "very much improved". Each of the Adderall groups was found to be significantly more improved than placebo using a Cochran-Mantel-Haenszel test adjusted for center. The Adderall 20, 40, and 60 mg groups had 23.3%, 29.6%, and 31.6% more improved patients than placebo, respectively.

3.1.7 Reviewer's Analysis

This reviewer verified the sponsor's analyses for the change from baseline to study end in the ADHD-RS total score (the primary endpoint) and the CAARS:S-S (a secondary endpoint). Datasets were not provided for the other secondary endpoints not associated with the ADHD-RS or CAARS.

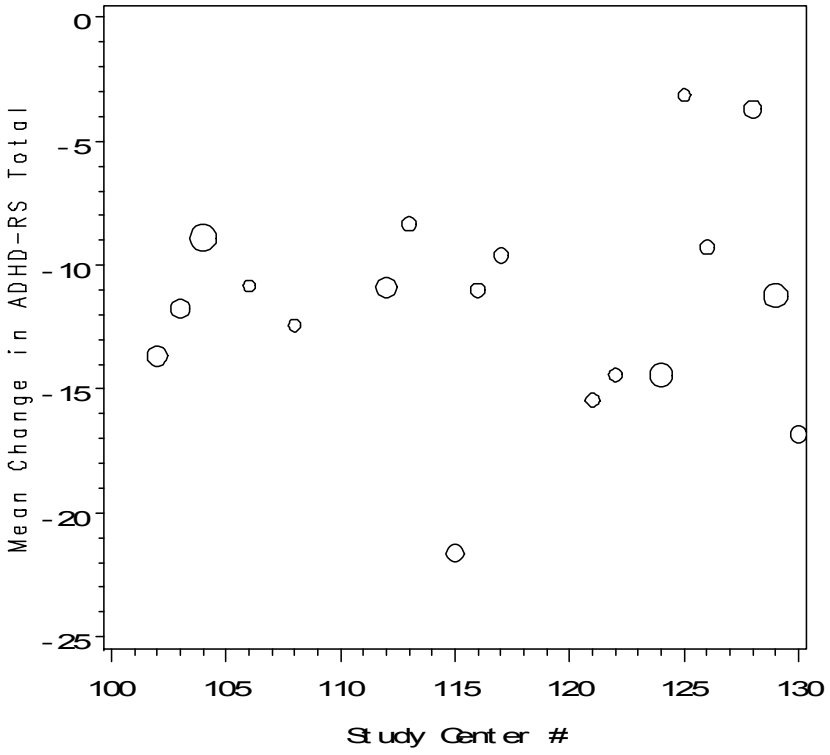
The sponsor's primary analysis method was an analysis of covariance for the ADHD-RS total score at the end of week 4 (or LOCF). The ANCOVA model included the baseline ADHD-RS as covariate and effects for treatment groups and centers. Because each dose was compared to placebo, Dunnett's method was used to protect the type I error. Since Dunnett's method depends on an assumption of normality this reviewer tested the residuals (differences between the observed responses and those predicted by the model) for normality using the Shapiro Wilk's test. The hypothesis of normality of the residuals was not rejected (p=0.25) so that Dunnett's method seems valid here. This reviewer then verified that each dose was significantly better than placebo for the primary endpoint using Dunnett's method to protect the type I error.

The center effects were significant (p=0.0005) indicating that there was a significant amount of variability in the center-specific mean changes from baseline. This means that some centers tended to rate patients higher (or lower) than others irrespective of the treatment group assignment (as seen in **F**igure 3.2). The average change from baseline ignoring treatment group was –11.7. An examination of the center-specific means shows that centers 115, 125, and 128 were the most atypical (i.e., had the largest absolute deviations from the average). The mean changes were -21.6, -3.1, and -3.7 respectively. Another distinguishing feature of center 128 was that the 60 mg dose group had a much larger improvement than each of the placebo, 20 mg, and 40 mg groups. Since these three centers stand out from the rest, we might investigate the effect of deleting them from the data. This makes the remaining center effects insignificant but all doses remain statistically superior to placebo. In addition, the ANCOVA model without center effects based on all the data leads to the same conclusion of efficacy. Thus, since the treatment effects are significant with or without center effects we need not be too concerned about the significance of the center effects.

Table 3.5 Centers with "Outlying" Mean Changes in ADHD-RS Total Score

Center	N	Base-line Mean	Change Mean
115	14	32.6	-21.6
125	7	27.1	-3.1
128	14	37.0	-3.7
All	248	32.0	-11.7

Figure 3.2 Center effects on Mean Change in ADHD-RS Total



The figure below suggests that there is more variability in the total score at endpoint for higher baseline scores than for lower baseline scores. Since higher baseline scores allow for more improvement this may be related to the limited range of the scale (0 to 54). One might be led to question the sensitivity of the scale since many subjects improved as much as the scale would allow. These maximal improvements also suggest that if the scale was continuous (could take on any value), as it is being modeled, the variability might be even larger. Dependence of the variance on

Figure 3.3 ADHD-RS Total Score vs. Baseline ADHD-RS Total Score

the baseline score would violate the assumption of identically distributed errors in the ANCOVA model, so we might consider a nonparametric alternative, like the Kruskal-Wallis test. This leads to

the same conclusion as the ANCOVA approach, so the treatment effects appear to have some robustness.

While each dose was significantly different from placebo at endpoint this reviewer does not believe there was a linear dose effect. It is true that the least squares means are ordered as would be required for a linear trend, but the differences between them are small compared to the variability. The Least Squares Means are –6.61, -7.17, and –7.78 with associated confidence intervals (-10.95,-2.27), (-11.52, -2.82), and (-12.19, -3.38). Notice that each of the three confidence intervals contains all three LSmeans. This suggests that, despite the ordering of the LSmeans, there is not a significant dose response trend. Another way to test this would be to compare the fit of two different models to the data. The first model attributes the same mean to each Adderall dose but a different mean to placebo. The second model uses a different mean for each dose and placebo. The first model was found to fit the data better so we conclude that there is no dose response trend.

Effect of Dropouts

Table 3.6 ITT and Observed Cases Analyses of ADHD-RS Total

		Population Member						
		No			Yes			
	Treatment Group	N	Baseline ADHD-RS	Change in ADHD-RS	N	Baseline ADHD-RS	Change in ADHD-RS	Dunnett P value
ITT	Placebo	.	.	.	60	33.0 (8.7)	-6.6 (11.1)	N / A
ITT	Add. XR 20	.	.	.	64	31.1 (9.6)	-12.6 (10.0)	0.0011
ITT	Add. XR 40	.	.	.	64	31.3 (8.1)	-12.9 (11.5)	0.0004
ITT	Add. XR 60	.	.	.	60	32.9 (9.8)	-14.3 (12.7)	0.0001
OC	Placebo	18	34.4 (8.8)	-0.6 (7.6)	42	32.4 (8.8)	-9.2 (11.4)	N / A
OC	Add. XR 20	17	33.7 (9.2)	-9.7 (9.7)	47	30.2 (9.7)	-13.7 (10.0)	0.0577
OC	Add. XR 40	15	30.9 (9.1)	-7.1 (9.6)	49	31.4 (7.9)	-14.7 (11.5)	0.0191
OC	Add. XR 60	15	32.1 (9.9)	-7.4 (9.9)	45	33.1 (9.9)	-16.7 (12.8)	0.0131

Although in each group dropouts did less well on average than completers the Observed Cases analyses and ITT-LOCF analyses produced consistent results except for the comparison of Adderall XR 20 and placebo. From Table 3.7 and Table 3.7 it appears that placebo dropouts did not due as well as placebo completers, but that, aside from those who dropped out at the end of week 2, Adderall XR 20 dropouts did nearly as well as Adderall XR 20 completers. This would suggest that the Observed Cases analysis, for which the Adderall XR 20 mg / Placebo comparison was not quite significant (p=0.058), may be biased against the Adderall XR 20 mg group. This seems to support

the LOCF analysis finding that Adderall XR 20 was statistically superior to placebo.

Table 3.7 Mean ADHD-RS Total Score for Dropouts and Completers

Last Week	Treatment Group	n	Week 0	Week 1	Week 2	Week 3	Week 4
Week 1	Placebo	4	35.0 (11.8)	35.0 (11.0)	.	.	.
Week 1	Add XR 20	6	33.8 (8.7)	20.3 (16.1)	.	.	.
Week 2	Placebo	11	34.4 (9.4)	34.7 (11.2)	33.8 (14.0)	.	.
Week 2	Add XR 20	7	29.7 (8.5)	19.6 (14.1)	24.7 (13.8)	.	.
Week 3	Placebo	3	34.0 (3.6)	24.7 (15.7)	39.0 (12.8)	32.7 (4.2)	.
Week 3	Add XR 20	4	40.5 (9.3)	29.3 (6.5)	24.0 (13.4)	28.3 (12.0)	.
Week 4	Placebo	42	32.4 (8.8)	26.3 (10.5)	25.9 (10.0)	23.5 (10.3)	23.2 (11.1)
Week 4	Add XR 20	47	30.2 (9.7)	21.3 (11.3)	19.1 (10.8)	17.4 (10.9)	16.5 (11.5)

Secondary Analyses

Recall that the CAARS:S-S ADHD index was to be collected at 4 and 12 hours post-dose, on Mondays, Wednesdays, and Fridays, in an attempt to assess the duration of effectiveness. For each week the three measurements taken at 4 hours (and separately for 12 hours) were to be averaged and the average for the last available week would be the basis for the treatment comparison. Many of the calls were not made on the designated days and many patients did not call on 3 days per week. In addition, many of the calls were not made close to the allotted times so the sponsor defined several time windows after the fact. For the ITT population at endpoint (LOCF), all doses were found to be significantly better than placebo for each of the four time windows. In the protocol the sponsor proposed comparing the high dose to placebo first, then the middle dose, and finally the low dose using a conditional testing procedure to control the type I error. However, they did not propose any adjustment for the two sets of multiple comparisons corresponding to the 4 hour and 12 hour data. One possibility would be testing the 4 hour data first and then testing the 12 hour data if all comparisons were significant for the 4 hour data. It seems that one should first test the data taken at 4 hours post dose to establish efficacy and then if efficacy is found proceed to test the 12 hour post-dose data. This reviewer verified the sponsor's results and they don't seem to depend on the order of testing chosen. However, 21 of the 248 patients could not be included in the analysis because they either had no baseline CAARS:S-S or no post-baseline CAARS:S-S. It is not clear how the data from these patients would have affected the results. In addition, for the study completers only the 60 mg dose was found to be significantly better than placebo at 4 or 12 hours post-dose. The study completers group sizes were 35, 44, 43, and 39 for placebo, 20 mg, 40 mg, and 60 mg respectively.

The sponsor also compared the CAARS:S-S scores at the end of each treatment week. At week 1 only the Adderall 60 mg group showed a significantly lower score ($p<0.05$), with the exception of 12 hours post-dose (9-16 hour time window) which showed no overall treatment effect. The improvement over placebo was not significant for the 40 mg group, and the test was not performed for the 20 mg group because of the closed testing procedure. At week 2, all Adderall XR groups showed significantly lower scores at both time points and windows. At week 3, Adderall XR 60 mg showed significantly lower scores at both time points and windows, while the 40 mg group showed a "trend towards significance" ($p<0.10$) and the 20 mg group showed significance only at 12 hours post-dose (10-14 hour time window). At week 4, the Adderall XR 60 mg group showed significantly lower scores at 4 hours post-dose while there was no overall treatment effect seen in the two-way ANCOVA at 12 hours. It was also noticed that if instead of the closed testing procedure, Dunnett's adjustment was used, as for the primary endpoint, then the 40 mg group would not be found significantly better than placebo at 4 hours using the 1-8 hour window.

(b) (4). First, many of the calls were not made very close to the designated times and no time windows were defined in the protocol. Also, the protocol stated that calls would be made on Mondays, Wednesdays,

and Fridays but many calls were made on other days. Second, 21 patients had insufficient data to be included in this analysis and it is not clear what effect they might have had on the analysis. Finally, although the treatment groups were superior to placebo at endpoint using the ITT population with the LOCF method, only the 60 mg group was found to be significant at 4 or 12 hours post-dose for the Observed Cases population.

3.2 Evaluation of Safety

See Clinical Review by Dr. Glenn Mannheim.

4. Findings in Special/Subgroup Populations

4.1 Gender, Race, and Age

4.1.1. Gender

The following table gives the Baseline ADHD-RS Total and the Change in ADHD-RS Total from baseline to endpoint (LOCF) by treatment group for males and females. Interestingly, the proportion of females increases as the Adderall XR dose increases. This situation could conceivably bias some of the treatment comparisons, but the results seem reasonably consistent for males and females. The p-value of the ANCOVA based test for a treatment/gender interaction was 0.64. This suggests that the treatment effects within the male and female subgroups were not significantly different. Yet, despite the suggestiveness of the differences in the means, none of the comparisons with placebo was significant in the subgroup of females. The insignificance may be due to the limited sample size in the female subgroup though.

Table 4.1 Mean ADHD-RS Total Score by Gender and Treatment

Level	Treatment Group	n	Baseline ADHD-RS Total	Change ADHD-RS Total
Male	Placebo	41	32.0 (8.6)	-6.0 (10.5)
Male	Add XR 20	41	30.8 (9.5)	-12.9 (10.4)
Male	Add XR 40	38	32.0 (8.0)	-11.6 (12.0)
Male	Add XR 60	29	32.6 (10.1)	-14.0 (12.5)
Female	Placebo	19	35.4 (8.7)	-8.0 (12.5)
Female	Add XR 20	23	31.7 (9.9)	-12.2 (9.5)

Female	Add XR 40	26	30.2 (8.3)	-14.8 (10.6)
Female	Add XR 60	31	33.1 (9.8)	-14.6 (13.1)

4.1.2. Race

Since most of the patients were White not much can be said about the treatment effects on other ethnicities. Interestingly though, the 7 subjects in the "other" category for race in the Adderall XR 60 mg group had an extraordinarily large average improvement. This group was comprised of 5 hispanics, 1 asian, and 1 native american. Four of the hispanics and the asian subject had the largest improvements in this group. Exclusion of these patients from the data did not alter the overall result.

Table 4.2 Mean ADHD-RS Total Score by Race and Treatment

Level	Treatment Group	n	Baseline ADHD-RS Total	Change ADHD-RS Total
White	Placebo	54	32.2 (8.3)	-6.6 (11.3)
White	Add XR 20	56	31.6 (9.1)	-13.2 (9.8)
White	Add XR 40	58	31.5 (8.2)	-13.1 (11.7)
White	Add XR 60	53	32.7 (9.9)	-13.2 (12.4)
Other	Placebo	6	40.2 (10.4)	-6.8 (10.2)
Other	Add XR 20	8	28.0 (12.8)	-8.3 (10.7)
Other	Add XR 40	6	29.0 (8.1)	-11.3 (9.4)
Other	Add XR 60	7	33.9 (10.1)	-22.9 (12.8)

4.1.3. Age

The treatment effects are reasonably similar in the Age < 40 and Age ≥ 40 subgroups (test for age group by treatment interaction p=0.39).

Table 4.3 Mean ADHD-RS Total Score by Age Group and Treatment

level	Treatment Group	n	Baseline ADHD-RS Total	Change ADHD-RS Total
Age < 40	Placebo	31	33.2 (9.3)	-7.7 (12.4)
	Adderall XR 20	32	32.9 (10.1)	-12.1 (10.8)
	Adderall XR 40	35	32.8 (8.2)	-14.5 (11.3)
	Adderall XR 60	33	33.0 (10.3)	-13.5 (13.0)
Age >= 40	Placebo	29	32.9 (8.2)	-5.4 (9.6)
	Adderall XR 20	32	29.4 (8.9)	-13.1 (9.3)
	Adderall XR 40	29	29.4 (7.7)	-11.0 (11.6)
	Adderall XR 60	27	32.7 (9.4)	-15.3 (12.5)

4.2. Other Special/Subgroup Populations

There were no analyses performed for other subgroups.

5. Summary and Conclusions

5.1 Statistical Issues and Collective Evidence

The primary analysis of this single 4 week randomized trial shows that Adderall XR 20 mg, 40 mg, and 60 mg groups were significantly better than placebo at endpoint based on the ADHD-RS Total score. Although in the Study Completers population the Adderall XR 20 mg /Placebo comparison was not quite significant at the 0.05 level (p=0.058), placebo completers seem to have done better than placebo dropouts so this analysis may be biased against the Adderall XR 20 mg group.

The CAARS:S-S ADHD index, a secondary endpoint, was to be assessed at 4 hours and 12 hours post-dose three times a week in an attempt to assess the duration of action. Although they are suggestive, the results of the CAARS:S-S analysis are less clear cut than the primary analysis results for several reasons. First, many of the calls were not made close to the designated times and no time windows were specified in the protocol. Second, 21 patients had insufficient data to be included in this analysis and it is not clear what effect they might have had on the analysis. Finally, although the treatment groups were superior to placebo at endpoint using the ITT population with the LOCF method, only the 60 mg group was found to be significant at 4 or 12 hours post-dose for the Observed Cases population.

5.2 Conclusions and Recommendations

The data and analysis from this single randomized double-blind, parallel-group design study support the efficacy of Adderall XR in adults.

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/s/

Tristan Massie
7/21/03 11:35:43 AM
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Kun Jin
7/21/03 02:44:41 PM
BIOMETRICS

George Chi
7/22/03 04:54:26 PM
BIOMETRICS

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

021303Orig1s005

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology and Biopharmaceutics Review

NDA: 21-303 (SE5-005; [redacted])
Drug: Mixed salts of a single entity amphetamine product [redacted] extended release capsules
Trade Name: Adderall XR®
Indication: Treatment of ADHD
Sponsor: Shire

Submission Type: General Correspondence- Response to FDA Approvable Letter
Submission Date: 2/13/04
Review Date: 6/17/04

Reviewer: Kofi A. Kumi, Ph.D.
Team Leader: Raman Baweja, Ph.D.

Background: The sponsor submitted a supplement for the use of Adderall XR for 1) treatment of adults with ADHD [redacted]. The sponsor received approvable letter on 10/17/03 which included questions from the Agency as well as labeling. This submission contains the responses to the Agency questions included in the approvable letter. The review focuses on the sponsor's responses to the clinical pharmacology and biopharmaceutics questions. In the approvable letter issued, responses to the following questions were requested by the Office of Clinical Pharmacology and Biopharmaceutics

OCPB Question 1

[redacted]

Sponsor's Response

Shire plans to submit to the Agency within 90 days of the approval letter [redacted]

Reviewer's comments

The sponsor's response is acceptable

OCPB Question 2

Please submit the mathematical model and the computations used [redacted]

Sponsor's Response

The sponsor's response to question 2 is attached.

Reviewer's Comments: The information provided in response to OCPB question 2 above is not sufficient. The sponsor should submit the control files, data files and any other information that will be needed to evaluate whether [redacted] *. It is preferred that the control files and data files are submitted electronically.*

OCPB Question 3

It is recommended that in future studies, the sponsor evaluate [redacted]

Sponsor's Response

Shire agrees with the Agency's recommendation and will evaluate [redacted]

Reviewer's Comments: The sponsor's response is acceptable

OCPB Question 4

Please adopt the following method and specification [redacted]

Apparatus: USP Apparatus II (paddle)
Speed of Rotation: 50 rpm
Media: Stage 1: pH 1.1 dilute HCL for 2 hours (750 mL) at 37 ? 0.5°C
Stage II: pH 6.0 phosphate buffer for 1 hour (950 mL) at 37 ? 0.5°C
Specifications: In 2 hours [redacted]
In 3 hours [redacted]

Sponsor's Response

Shire confirms that the method and specification described above will be adopted [redacted]

Reviewer's comments: The sponsor's response is acceptable

Comment to Sponsor

1) *The sponsor should submit the control files, data files and any other information that will be needed to evaluate whether the* [redacted] *. It is preferred that the control files and data files are submitted electronically*
2) *It is recommended that the sponsor incorporates the changes in the clinical pharmacology and dosage and administration sections of the revised proposed label (See attached label)*

Kofi A. Kumi, Ph.D._____

RD/FT Initialed by Raman Baweja, Ph.D._____

CC: NDA 21-303 SE5-005, (b) (4) HFD-120, HFD-860 (Mehta, Sahajwalla, Baweja, Kumi), CDR (Biopharm)

Appendix

Sponsor's Response to OCPB Question 2

Revised Proposed Label

2

1 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

13 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page.

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/s/

Kofi Kumi
6/21/04 04:29:38 PM
BIOPHARMACEUTICS

Raman Baweja
6/21/04 05:31:21 PM
BIOPHARMACEUTICS

Clinical Pharmacology and Biopharmaceutics Review

NDA:	21-303 SE5-005, (b) (4)
Generic Name:	Mixed salts of a single entity amphetamine product
Trade Name:	Adderall XR®
Dosage Strengths:	(b) (4) extended release capsules
Sponsor:	Shire
Indication of Drug:	Treatment of Attention-Deficit/Hyperactivity Disorder (ADHD) in Adults
OND Clinical Division:	Division of Neuropharmacological Drug Products (HFD-120)
OCPB Division:	Division of Pharmaceutical Evaluation 1 (HFD-860)
Submission Type:	Efficacy (b) (4)
Submission Dates:	12/18/2002, 3/27/03, 6/20/2003, 7/25/2003
Reviewer:	Kofi A. Kumi, Ph.D.
Team Leader:	Raman Baweja, Ph.D.

Executive Summary

Synopsis: The sponsor is seeking approval of Adderall XR for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in adults. Adderall XR is already approved for ADHD in children. Adderall XR is currently available as 5, 10, 15, 20, 25, 30 mg strengths. In the efficacy trial for this supplement, the sponsor studied doses up to 60 mg Adderall XR by using multiples of the approved strengths. (b) (4) The supplemental NDA contains the results of one controlled efficacy study, an interim analysis of a long term safety study, a pharmacokinetic dose proportionality study, (b) (4) and a reference to 2 previously conducted food effect (SLI 381.102 and SLI 381. 103) and a multiple dose (SLI 381.105) studies submitted to the original NDA (21-303). (b) (4) (b) (4)

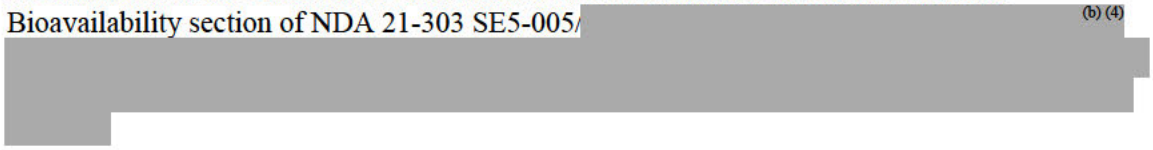
Adderall XR is a modified release formulation of an approved immediate release (IR) formulation, Adderall. Adderall XR was developed to facilitate once a day dosing for treatment of ADHD. Both Adderall IR and Adderall XR contain d-amphetamine and l-amphetamine salts in a ratio of 3:1. Amphetamines are non-catecholamine sympathomimetic amines with CNS stimulant activity. Oral administration of Adderall XR delivers a dose of mixed amphetamine salts via a two pulse release. The capsules contain two types of pellets: immediate release pellets that release the first half of the dose of mixed amphetamine salts in a similar mechanism to Adderall IR, and delayed-release pellets that release the second half of the dose of mixed amphetamines salts 4 to 6 hours later.

In the review of the original NDA (21-303), OCPB concluded that food does not affect the pharmacokinetics of d- and l-amphetamine after administration of Adderall XR 30 mg, the highest approved strength. Linear relationship was observed for Cmax and AUC over the dosage range of 10 to 30 mg of Adderall XR after multiple doses. There was no unexpected accumulation in pediatric patients. In across studies comparison, the mean accumulation factor

(the ratio of AUC(0-24h) at steady state to AUC(0-24h) after single dose) in adults was 1.44 for d-amphetamine and 1.64 for l-amphetamine.

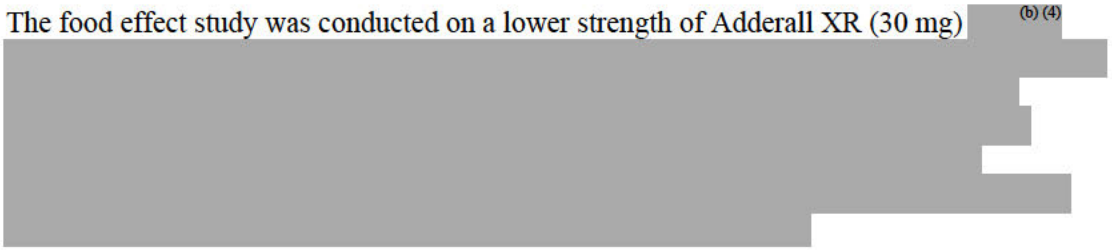
In an open-label, randomized, single-dose, three-treatment, and three-period crossover dose proportionality study, 12 subjects were given a single oral dose of either Adderall XR 2 x 10 mg capsules or Adderall XR 2 x 20 mg capsules or Adderall XR 2 x 30 mg capsules orally after a 10-hour overnight fast. The results of the study indicated that AUC and Cmax were linearly proportional to dose in the range from 20 to 60 mg when given as single doses of 2x 10 mg, 2 x 20 mg and 2 x 30 mg.

Recommendation: Based on the data submitted to the Human Pharmacokinetics and Bioavailability section of NDA 21-303 SE5-005/

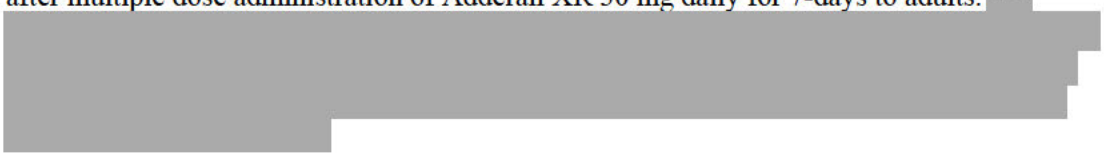


General Comments

1) The food effect study was conducted on a lower strength of Adderall XR (30 mg)



2) In an across studies comparison in the original application, moderate accumulation (accumulation ratio of 1.44 for d-amphetamine and 1.64 for l-amphetamine) was observed after multiple dose administration of Adderall XR 30 mg daily for 7-days to adults.



3)

Comments to Sponsor

1) [redacted] (b) (4)

2) [redacted] (b) (4)

3) It is recommended that in future studies, the sponsor evaluate the [redacted] (b) (4) .

4) The sponsor should adopt the following method and specification [redacted] (b) (4) of Adderrall XR.

Apparatus:	USP Apparatus II (paddle)
Speed of Rotation	50 rpm
Media: Stage 1:	pH 1.1 dilute HCL for 2 hours (750 mL) at 37 ± 0.5°C
Stage 2:	pH 6.0 Phosphate buffer for 1 hour (950 mL) at 37 ± 0.5°C
Specifications:	In 2 hours, [redacted] (b) (4)
	In 3 hours, [redacted] (b) (4)

5) Please forward comments 1 – 4 and labeling recommendations (see below) to sponsor.

Labeling Recommendations:

The following suggested changes by the sponsor to the Clinical Pharmacology section are acceptable to OCPB. OCPB recommended additions are double underlined and deletions are strikeout

Clinical Pharmacology Section

The mean elimination half-lives for d-amphetamine and l-amphetamine in adults are 10 hours and 13 hours respectively. In children aged 6 to 12 years, the mean elimination half-life is 1 hour shorter for d-amphetamine (9 hours) and 2 hours shorter for l-amphetamine (11 hours). Children had higher systemic exposure to amphetamine (Cmax and AUC) than adults for a given dose of Adderall XR, which was attributed to the higher dose administration to children on a mg/kg body

weight basis compared to adults. Upon dose normalization on a mg/kg basis, children showed 30% less systemic exposure compared to adults.

Adderall XR demonstrates linear pharmacokinetics over the dose range of 20 to 60 mg in adults and 5mg to 30 mg in children aged 6 to 12 years. There is no unexpected accumulation at steady state in children

Food does not affect the extent of absorption of *d-amphetamine and l-amphetamine* [redacted] but prolongs Tmax by [redacted] 2.5 hours (from 5.2 hrs at fasted state to 7.7 hrs after a high-fat meal *for* [redacted] *l-amphetamine* [redacted] *after administration of Adderall XR 30 mg. Equal doses of Adderrall XR strengths are bioequivalent.*

Kofi A. Kumi, Ph.D._____

RD/FT Initialed by Raman Baweja, Ph.D._____

CC: NDA: 21-303SE5-005, [redacted] HFD-120, HFD-860 (Mehta, Sahajwalla, Baweja, Kumi), CDR (Biopharm.)

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/s/

Kofi Kumi
8/4/03 11:30:53 AM
BIOPHARMACEUTICS

Raman Baweja
8/4/03 12:52:23 PM
BIOPHARMACEUTICS
Adderall XR -- review of (b) (4) the efficacy supplement (b) (4)

Office of Clinical Pharmacology and Biopharmaceutics

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	**21—303 S005**	**Brand Name**	**Adderall XR**
OCPB Division (I, II, III)	**I**	**Generic Name**	**Mixed salts of amphetamine**
Medical Division	**DNDP (HFD-120)**	**Drug Class**	**CNS Stimulant**
OCPB Reviewer	**Kofi Kumi**	**Indication(s)**	**Attention Deficit Hyperactivity Disorder (ADHD)**
OCPB Team Leader	**Raman Baweja**	**Dosage Form**	**5 (b) (4) mg extended release capsules.** (b) (4)
		Dosing Regimen	**5- 30 mg/day for children 20 (b) (4) mg/day for adults**
Date of Submission	**12/15/02**	**Route of Administration**	**Oral**
Estimated Due Date of OCPB Review	**9/15/03**	**Sponsor**	**Shire Pharmaceuticals**
PDUFA Due Date	**10/15/03**	**Priority Classification**	**Standard**
Division Due Date	**9/15/03**		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	**Number of studies submitted**	**Number of studies reviewed**	**Critical Comments If any**
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables data, etc.	**X**			
Tabular Listing of All Human Studies	**X**			
HPK Summary	**X**			
Labeling	**X**			
Reference Bioanalytical and Analytical Methods	**X**			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	**X**	**1**		Via cross reference to original NDA 21-303
multiple dose:	**X**	**1**		Via cross reference to original NDA 21-303
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:	**X**	**1**		
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				.
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				

pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics		1111111111111111111111111111		
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:	**X**	**1**		Study conducted in pediatric volunteers ages 7-12 years old
replicate design; single / multi dose:				
Food-drug interaction studies:	**X**	**1**		Via cross reference to original NDA 21-303
Dissolution:	**X**	**1**		Dissolution profile comparison for 5, 10, 15, 20, 25, 30 (b) (4) mg capsules XR
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		**3**		

Filability and QBR comments				
	"X" if yes	**Comments**		
Application filable ?	**X**	Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?		
Comments sent to firm ?		Comments have been sent to firm (or attachment included). FDA letter date if applicable.		
QBR questions (key issues to be considered)	**1.** (b) (4) **2.** (b) (4) **3.** (b) (4) **4.** (b) (4) **?** **5.** (b) (4)			
Other comments or information not included above				
Primary reviewer Signature and Date				
Secondary reviewer Signature and Date				

CC: NDA 20-303 SE5-005, HFD-850 (Electronic Entry or Lee), HFD-120, HFD-860 (Baweja, Sahajwalla, Mehta)), CDR-Biopharm.

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/s/

Kofi Kumi
2/14/03 02:20:20 PM
BIOPHARMACEUTICS
Filing memo

Raman Baweja
2/14/03 03:10:53 PM
BIOPHARMACEUTICS
Filing Memo

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

021303Orig1s005

OTHER REVIEW(S)

DEPARTMENT OF HEALTH & HUMAN SERVICES **Public Health Service**

Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
Food and Drug Administration
Rockville MD 20857

CLINICAL INSPECTION SUMMARY

DATE: July 29, 2003

TO: Anna Marie Homonnay-Weikel, R.Ph., Regulatory Project Manager
Glenn Mannheim, M.D., Medical Officer
Division of Neuropharmacological Drug Products, HFD-120

THROUGH: Khin Maung U, M.D., Branch Chief
Good Clinical Practice Branch I, HFD-46
Division of Scientific Investigations

FROM: Ni A. Khin, M.D., Medical Officer
Good Clinical Practice Branch I, HFD-46
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspection

NDA: NDA 21-303/SE-5-005

APPLICANT: Shire Pharmaceutical Development, Inc.

DRUG: Adderall XR (extended release capsule of mixed salts of a single entity amphetamine product)

THERAPEUTIC CLASSIFICATION: Type S, Standard Review

INDICATION: Treatment of Attention Deficit Hyperactivity Disorder (ADHD) in Adults

CONSULTATION REQUEST DATE: February 10, 2003

ACTION GOAL DATE: October 18, 2003

I. BACKGROUND:

Adderall XR (extended release capsule of mixed salts of a single-entity amphetamine product) has been approved for the treatment of attention deficit hyperactivity disorder (ADHD) in children aged 6-12 years. In this application, the sponsor has requested the use of Adderall XR in treatment of ADHD in adults. The application is based on the results from protocol SLI 381-303 entitled " a randomized, double-blind, placebo-controlled, parallel-group study of Adderall XR in adults with attention deficit hyperactivity disorder."

The protocol is a multi-center, randomized, double-blind, placebo-controlled, parallel-group study of 4 weeks' duration of the efficacy and safety of three doses (20, 40 or 60 mg given once daily) of Adderall XR compared to placebo in adults with ADHD. Subjects were screened for a 1-week period prior to washout. Subjects then had a 1-week washout of prior ADHD therapy between visit 1 screening and visit 2 baseline. Eligible subjects were randomized to either Adderall XR or placebo for 4 weeks. Primary efficacy measure used was the ADHD-Rating Scale (ADHD-RS) scores. The scale used was an 18-item scale of ADHD symptoms (0=none to 3=severe) revised for adults with ADHD; completed by the subject with a clinician with reference to their ADHD symptoms the week prior. ADHD-RS was provided to the investigators to aid in judging disease severity and change in illness to completed CGI-S and CGI-C ratings respectively.

Inspection assignment was issued in March 2003 for 2 sites: Drs. Kelsh and Toups. These clinical investigators were one of the higher enrollers in the study.

II. RESULTS (by site):

NAME	CITY	STATE	ASSIGNED DATE	EIR RECEIVED DATE	CLASSIFICATION
Dr. Kelsh	Overland Park	KS	03-06-2003	05-05-2003	NAI
Dr. Toups	Lafayette	CA	03-06-2003	06-16-2003	NAI

KELSH, M.D.

At this site, a total of 21 subjects were randomized; 18 subjects completed the study and three subjects discontinued from the study. Subject 112-008 assigned to placebo withdrew consent; subject 112-005 from Adderall XR 20mg group was discontinued due to protocol violation, particularly, alcohol abuse and subject 112-025 from Adderall XR 40mg group was discontinued due to lack of efficacy.

An audit of all subjects' records was conducted. No FDA-483 was issued. No major compliance issue noted. Data appear acceptable.

TOUPS, M.D.

At this site, 27 subjects were screened and 4 were listed as screen failures. A total of 23 subjects were randomized and 17 subjects completed the study. Six subjects receiving Adderall XR (20, 40 or 60 mg) discontinued from the study because of adverse events. Specifically, subject 001 had agitation; subject 003 reported irritability; subject 011 reported having elevated BP; subject 006 and 019 had insomnia; and subject 009 experienced chest pain.

An audit of all subjects' records was conducted. No FDA-483 was issued. No major compliance issue noted. It was reported that the source documents and CRFs generally agreed with data listings. Data appear acceptable.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

For the study sites that were inspected, there was sufficient documentation to assure that all audited subjects did exist, fulfilled the eligibility criteria, that all enrolled subjects received the assigned study medication, and had their primary efficacy endpoint captured as specified in the protocol and amendments. Overall, the data from these sites inspected appear acceptable for use in support of this pending supplemental NDA.

Key to Classifications
NAI = No deviation from regulations. Data acceptable
VAI = Minor deviations(s) from regulations. Data acceptable
VAIr= Deviation(s) form regulations, response requested. Data acceptable
OAI = Significant deviations for regulations. Data unreliable
Pending = Inspection not completed

_____
Ni A. Khin, M.D., Medical Officer
Good Clinical Practice Branch I, HFD-46
Division of Scientific Investigations

CONCURRENCE:

_____
Khin Maung U, M.D, Branch Chief
Good Clinical Practice Branch I, HFD-46
Division of Scientific Investigations

cc:
NDA 21-303/SE5-005
Division File
HFD-45/Program Management Staff (electronic copy)
HFD-46/U
HFD-46/Khin
HFD-46/Friend
HFD-46/George GCPB1 Files

rd:NK:07/29/03

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/s/

Ni Aye Khin
7/29/03 11:36:05 AM
MEDICAL OFFICER

Khin U
7/29/03 11:49:20 AM
MEDICAL OFFICER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

021303Orig1s005

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY FOR NDA # _21-303__SUPPL #_005_____

Trade Name _Adderall XR

Generic Name mixed salts of a single entity amphetamine product

Applicant Name Shire Pharmaceutical Development Inc. HFD # 120

Approval Date If Known _August 11, 2004

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?
YES /__X_/ NO /___/

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

_SE 5_____

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES /_X__/ NO /___/

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

_____

_____

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

_____

_____

d) Did the applicant request exclusivity?

YES /_X__/ NO /___/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

_____3 years_____

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /___/ NO /__X_/

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Writen Request?

_____

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES /___/ NO /__X_/

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved.

Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /_X__/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 21-303 Adderall XR (mixed salts of a single entity amphetamine product

NDA# _____ _____

NDA# _____ _____

2. Combination product. N/A

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /__/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____ _____

NDA# _____ _____

NDA# _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.) IF "YES" GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or

supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /_X__/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /_X__/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

_____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /_X__/ NO /___/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /_X__/

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product? N/A

YES /___/ NO /___/

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

SLI381.303 and SLI.381.304

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously

approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /_X__/

Investigation #2 YES /___/ NO /_X__/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

_____ _____

_____ _____

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /__X_/

Investigation #2 YES /___/ NO /_X__/

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

_____ _____

_____ _____

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in

#2(c), less any that are not "new"):

SLI381.303 and SLI.381.304

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # 58,037 YES /_X__/ NO /___/ Explain: _____

Investigation #2

IND # 58,037 YES /_X__/ NO /___/ Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES /___/ Explain _____ NO /___/ Explain _____

Investigation #2

YES /___/ Explain _____ NO /___/ Explain _____

!
_____ ! _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /__X_/

If yes, explain: _____

_____

Signature Richardae Taylor, Pharm.D. Date 8/24/04
Title: Regulatory Project Manager

Signature of Office/
Division Director

Russell Katz, M.D.
Director, Division of Neuropharmacological Drug Products

See electronic signature below

Form OGD-011347 Revised 05/10/2004

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/s/

Russell Katz

12/1/04 08:06:44 AM

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA # : 21-303 **Supplement Type (e.g. SE5):** SE 5 **Supplement Number:** 005

Stamp Date: December 18, 2002 **Action Date:** August 11, 2004

HFD 120 **Trade and generic names/dosage form:** Adderall XR (mixed salts of a single entity amphetamine product) Extended-Release Capsules

Applicant: Shire Pharmaceutical Development Inc. **Therapeutic Class:** amphetamine

Indication(s) previously approved: ADHD (in children)

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 1

Indication #1: Adult ADHD

Is there a full waiver for this indication (check one)?

- ❑ **Yes: Please proceed to Section A.**

X No: Please check all that apply: ____**Partial Waiver** ____**Deferred** _X_**Completed**
NOTE: More than one may apply
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ❑ **Products in this class for this indication have been studied/labeled for pediatric population**
- ❑ **Disease/condition does not exist in children**
- ❑ **Too few children with disease to study**
- ❑ **There are safety concerns**
- ❑ **Other:**_____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min_____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____
Max_____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____

Reason(s) for partial waiver:

- ❑ **Products in this class for this indication have been studied/labeled for pediatric population**
- ❑ **Disease/condition does not exist in children**
- ❑ **Too few children with disease to study**
- ❑ **There are safety concerns**
- ❑ **Adult studies ready for approval**
- ❑ **Formulation needed**

❑ **Other:**_____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____
Max_____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____

Reason(s) for deferral:

- ❑ **Products in this class for this indication have been studied/labeled for pediatric population**
- ❑ **Disease/condition does not exist in children**
- ❑ **Too few children with disease to study**
- ❑ **There are safety concerns**
- ❑ **Adult studies ready for approval**
- ❑ **Formulation needed**

Other:_____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies: Original NDA approved in pediatric population, children with ADHD aged 6-12 years. See comments below.

Min _____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____
Max_____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____

Comments: Pending efficacy supplement for use of Adderall XR in adolescents aged 13-17 years (NDA 21-303/S-009).

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

_____
Regulatory Project Manager

cc: NDA 21-303
HFD-960/ Grace Carmouze

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

(revised 12-22-03)

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: _____

Is there a full waiver for this indication (check one)?

- ❑ **Yes: Please proceed to Section A.**

- ❑ **No: Please check all that apply: ____Partial Waiver ____Deferred ____Completed**
  NOTE: More than one may apply
  Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ❑ **Products in this class for this indication have been studied/labeled for pediatric population**
- ❑ **Disease/condition does not exist in children**
- ❑ **Too few children with disease to study**
- ❑ **There are safety concerns**
- ❑ **Other:_____**

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Reason(s) for partial waiver:

- ❑ **Products in this class for this indication have been studied/labeled for pediatric population**
- ❑ **Disease/condition does not exist in children**
- ❑ **Too few children with disease to study**
- ❑ **There are safety concerns**
- ❑ **Adult studies ready for approval**
- ❑ **Formulation needed**
- ❑ **Other:_____**

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Reason(s) for deferral:

- ❑ **Products in this class for this indication have been studied/labeled for pediatric population**
- ❑ **Disease/condition does not exist in children**
- ❑ **Too few children with disease to study**
- ❑ **There are safety concerns**
- ❑ **Adult studies ready for approval**
- ❑ **Formulation needed**
- ❑ **Other:_____**

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Comments:

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

cc: NDA 21-303
HFD-960/ Grace Carmouze

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

(revised 10-14-03)

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/s/

Russell Katz
12/1/04 08:02:50 AM

Taylor, Richardae

From: Taylor, Richardae
Sent: Thursday, October 14, 2004 3:41 PM
To: 'LaPree, Charles'
Subject: Response to Information Request

Hi Chuck,
Please refer to your correspondence dated October 6, 2004 to NDA 21-303/S-005 for Adderall XR requesting clarification from the Division regarding a comment in our approval labeling for Adderall XR (dated August 11, 2004). We have provided below information from the Office of Drug Safety that supports the comment made in our labeling.

FDA Comment in the Adderall XR approval labeling for S-005 under Warnings, Sudden Death and Pre-existing Structural Cardiac Abnormalities:

"[Our review of sudden death in the pediatric age group revealed that 6/12 had structural cardiac defects]"

Information to support this statement from the Office of Drug Safety is provided in a word copy attached below.

structural
diac abnormalit

Kind regards,
Chardae

****

Richardae C. Taylor, Pharm.D., LT USPHS
Regulatory Project Manager
Division of Neuropharmacological Drug Products, HFD-120
Center For Drug Evaluation and Research, FDA
Office of Drug Evaluation I
Ph: (301) 594-5793
Fax: (301) 594-2859
Email: taylorr@cder.fda.gov

Pediatric Sudden Death Cases Associated with Amphetamine Therapy

Comprehensive searches of the AERS safety database were performed to identify deaths in pediatric patients (ages 1 to 18 years) treated with amphetamine. Reports were excluded from the analysis if death was caused by intoxication with multiple drugs, if drug abuse was reported, if the death was most likely caused by another condition or drug, or if the specifics of the case were not consistent with usual therapeutic use of the drug (e.g., intravenous or intranasal administration of a drug intended for oral use). Non-excluded cases were further reviewed to identify domestic cases of sudden death which were received by the FDA during the five year period between January 1, 1999 and December 31, 2003. For the purposes of this analysis, sudden death cases were identified that were consistent with a World Health Organization (WHO) definition (i.e., death is instantaneous, or occurs within 24 hours of an acute collapse).[1]

Twelve (12) pediatric sudden death cases were identified in this analysis. The suspect drug was reported as Adderall or Adderall XR in each of these cases. The cases were reviewed for potential identifiable risk factors. Of the total, five (5) cases included information about autopsy results which indicated a finding of a structural cardiac abnormality.

These findings included:

- bicuspid aortic valve (3811155-1),
- idiopathic hypertrophic subaortic stenosis and cardiomegaly (3782505-X),
- chronic cardiac hypertrophy (3887728-7),
- "increased density of the muscle around the heart" (3555682-3),
- "aberrant origin of right main coronary around aorta and embedded in fibrous tissue" (4223562-6).

In one additional case (4163447-7), a maternal history of ventricular tachycardia treated with implanted defibrillation and ablation was reported.

Narrative summaries of the available information for these six cases are presented below:

Structural cardiac abnormalities:

3811155-1/US (3723113): A pediatrician reported that a 7 year old male with a history of heart murmur died suddenly during therapy with Adderall (dose, duration of therapy, and indication not reported). The child was found dead in his bed on (b) (6) Autopsy showed bicuspid aortic valve and no other abnormalities. The "tox screen was negative for amphetamines". The coroner considered that the child died of an arrhythmia.

3782505-X/US (3701541) (dup 3859036-1): A pediatrician reported that a 13 year old male collapsed while working at his computer and died suddenly after taking a single dose of Adderall 20 mg for the treatment of ADHD. He had been seen by a physician for a physical exam the previous day, with complaints of school problems and was diagnosed with ADHD. Blood pressure and heart rate were normal. Weight was 118 pounds. He was active in sports. The patient took a single dose of Adderall 20 mg at 10:30 am, complained of tiredness about midday, and collapsed at his computer in late afternoon. A pulse was

[1] Roberts, WC. Sudden cardiac death: definitions and causes. *Am J Cardiol* 1986; **57**: 1410-13.

present when emergency personnel arrived, but he was pulseless at the hospital. An autopsy showed idiopathic hypertrophic subaortic stenosis (IHSS), "apparently a genetic disorder", and an enlarged heart "filling complete chest". The number of Adderall tablets was correct in the remaining drug supply. No concomitant medications were reported. Final pathology report and drug screening results were not provided. The reporting physician considered that the cause of death was cardiomegaly (unrelated to Adderall), and arrhythmia possibly caused by Adderall.

3887728-7/US (3776530): [redacted] and a medical examiner reported that a 14 year old male developed shortness of breath while running, followed by collapse and full cardiac arrest after approximately four years of therapy with Adderall (dose not specified) for the treatment of ADHD. [redacted]. Prior therapy included Ritalin (dose and duration of therapy not reported). Autopsy showed the heart weighed 315 grams. The coroner stated that the expected cardiac weight for this child's body weight is 206-299 grams, and the expected cardiac weight for the child's age is 213-237 grams. Heart blood amphetamine level was 0.22 mg/L. Mild ventricular hypertrophy was noted, and was concentric, with no definite septal asymmetry noted. Microscopic examination showed "equivocal evidence of myocardial cell hypertrophy." Postmortem diagnosis was "Sudden collapse and death of 14 year old male during exercise class at school; past history of cardiac murmur diagnosed as a functional murmur; short history of dyspnea prior to terminal collapse; cardiac hypertrophy; pulmonary congestion and edema; no evidence of trauma; history of treatment with Adderall (amphetamine) for attention deficit disorder, treatment lasted several years; toxicological examination (heart blood) positive for amphetamine." The coroner concluded that the cause of death was "cardiac hypertrophy, years, due to chronic amphetamine toxicity, years, due to Adderall therapy, years." The coroner commented that "the subject died as a result of a cardiac arrhythmia due to amphetamine-related cardiac hypertrophy. The level of amphetamine in the blood at the time of death was higher than would be generally expected with a therapeutic dose."

3555682-3/US (3521975): A [redacted] and the father of the patient reported that a 15 year old male collapsed while [redacted], and was subsequently pronounced dead at the hospital after approximately three years of therapy with Adderall 20 mg for the treatment of ADD. The child's father stated that the cause of death was explained to him as "an arrhythmia caused by an increased density of the muscle around the heart", and that "neither the family physician nor the medical examiner considered Adderall a suspect in his son's death." Since his son had been asymptomatic, "the condition remained undiagnosed". The child had "appeared healthy during a recent sports physical." His son was an honor student with no history of drug abuse. Medical history included an unspecified "heart murmur" which had been diagnosed at age nine months, which was followed by the physicians until it was felt to have "resolved" at age two years. There is no family history of cardiac disease.

4223562-6/US (4029308) (dup 4258509-X): A reviewing psychiatrist [redacted] reported that a 12 year old male with a history of bipolar disorder, oppositional defiant disorder, and other unspecified conditions, experienced a fatal myocardial infarction during therapy with ADDERALL immediate release formulation 15 mg twice daily. Total duration of therapy was not specified, but the reporter stated that the dose had been increased to 15 mg twice daily "several months prior to his death". [redacted] His "cardiac enzymes were increased at the 1 am blood draw". At 5:30 am on [redacted], the "wall of his heart blew out and CPR was performed". The child died. An autopsy showed "aberrant origin of right main coronary around aorta and embedded in fibrous tissue". The reporter stated that the child had experienced "palpitations and dizziness at the lower dose", and there had been "at least one episode of tachycardia during treatment (not followed well)". Reportedly, his "general practitioner had wanted cardiac studies but did not share this information with the prescribing psychiatrist". The child had a pre-existing cardiac malformation which was not known. No information was provided pertaining to concomitant medications.

Maternal history of ventricular arrhythmia:

4163447-7/US (3985139) (dup 3972359-0): A pediatrician reported via a sales representative that a 12 year old male died suddenly on [redacted] after taking a single dose of Adderall XR 10 mg for the treatment of ADHD. Previous treatment for ADHD included Ritalin (methylphenidate) for about four years

(dose not reported). Medication was changed to Adderall XR 10 mg, and the child took his first dose on (b) (6) At about 4 pm that day, he collapsed while running cross country. He had run about one to two miles. He could not be revived. Autopsy results were not reported. Family history was positive for maternal arrhythmia (ventricular tachycardia treated with implanted defibrillation and ablation) which the child's mother had developed about three years prior. The death certificate indicated the cause of death was sudden cardiac death.

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/s/

Richardae Taylor

10/14/04 03:47:34 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

JUN 26 2003

Kathleen Toups, M.D.
Bay Area Research Institute
3736 Mt. Diablo Blvd., Suite 204
Lafayette, California 94598

Dear Dr. Toups:

Between April 28 and May 7, 2003, Mr. Jeffrey W. Shrifter, representing the Food and Drug Administration (FDA), conducted an investigation and met with you to review your conduct of a clinical investigation (protocol SLI 381-303 entitled: "A randomized, double-blind, placebo-controlled, parallel-group study of Adderall XR in adults with attention deficit hyperactivity disorder") of the investigational drug Adderall XR (extended- release capsule of mixed salts of a single-entity amphetamine product), performed for Shire Pharmaceutical Development, Inc. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to monitor the conduct of research and to ensure that the rights, safety, and welfare of the human subjects of those studies have been protected.

From our evaluation of the establishment inspection report and the documents submitted with that report, we conclude that you adhered to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations and the protection of human subjects.

We appreciate the cooperation shown Investigator Shrifter during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely yours,

Antoine El-Hage

Antoine El-Hage, Ph.D.
Associate Director
Good Clinical Practice Branch I & II, HFD-46/47
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place, Room 125
Rockville, MD 20855

FEI: 3003955844
Field Classification: NAI
Headquarters Classification:
__X__1)NAI
_____2)VAI- no response required
_____3)VAI- response requested
_____4)OAI

cc:
HFA-224
HFD-120 Doc.Rm. NDA 21-303/SE5-005
HFD-120 Review Div.Dir. Katz
HFD-120 MO Mannheim
HFD-120 PM Homnnay-Weikel
HFD-47 c/r/s GCP File #10927
HFD-47 MO Khin
HFD-47 CSO Friend
HFR-PA150 DIB Moss
HFR-PA150 BIMO Almogela
HFR-PA150 Field Investigator Montgomery
GCF-1 Seth Ray

r/d:NK: 6/17-6/18/03
reviewed:AEH:6/19/03
f/t:ml:6/23/03

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Reviewer Note to Rev. Div. M.O.

- For this study, 27 subjects were screened and 4 were listed as screen failures. A total of 23 subjects were randomized and 17 subjects completed the study. Six subjects receiving Adderall XR (20, 40 or 60 mg) discontinued from the study because of adverse events. Specifically, subject 001 had agitation; subject 003 reported irritability; subject 011 reported having elevated BP; subject 006 and 019 had insomnia; and subject 009 experienced chest pain.
- An audit of all subjects' records was conducted. No FDA-483 was issued. No major compliance issue noted. It was reported that the source documents and CRFs generally agreed with data listings.
- Data appear acceptable.

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/s/

Joseph Salewski
7/1/03 10:31:17 AM

Homonnay Weikel, Anna M

From: Homonnay Weikel, Anna M
Sent: Friday, June 27, 2003 10:47 AM
To: 'DAleknavage@us.shire.com'
Cc: Homonnay Weikel, Anna M
Subject: FW: re: FDA Request for Info re: NDA 21-303/S-005

Hi Debbie:
In addition to the request below that I forwarded last week some new questions related to adverse event reports have come up. Our request for info is delineated below:

1. Please provide the total exposure since approval for both Adderall IR and XR in adults and separately for children.
2. Based upon our review of the adverse events reports for NDA 21-303 since approval 10-11-01, we have identified 7 reports that have been submitted. Please confirm that this is a complete listing.
3. Please provide a cumulative listing of all serious and non-serious adverse events for Adderall XR.

Thanks Alot

Anna Marie H. Weikel, R.Ph.
Divison of Neuropharmacological Drug Products
Office of Drug Evaluation I
FDA Center for Drug Evaluation and Research
Senior Regulatory Project Manager
(301) 594-5535

-----Original Message-----
From: Homonnay Weikel, Anna M
Sent: Friday, June 20, 2003 9:27 AM
To: 'DAleknavage@us.shire.com'
Subject: re: FDA Request for Info re: NDA 21-303/S-005

Debbie:
The medical reviewer has requested the following below. If it is located in the submission, please indicated where.

1) a summary and a discussion of the post-marketing experiences of Adderall XR and Adderall in adults and differences with post-marketing experiences with children;
2) and a literature review dealing with the AE's.

Thanks,

Anna Marie H. Weikel, R.Ph.
Divison of Neuropharmacological Drug Products
Office of Drug Evaluation I
FDA Center for Drug Evaluation and Research
Senior Regulatory Project Manager
(301) 594-5535

APPEARS THIS WAY ON ORIGINAL

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/s/

Anna-Marie Homonnay
6/27/03 10:51:16 AM
CSO

Anna-Marie Homonnay
6/27/03 10:53:15 AM
CSO

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION	REQUEST FOR CONSULTATION
TO (Division/Office) DDRE/ODS **HFD 430**	**FROM:** **HFD-120/NEUROPHARMACOLOGIC DRUG PRODUCTS**

Date 6/23/03	**IND No.**	**NDA No.** 21-303	**TYPE OF DOCUMENT**	**DATE OF DOCUMENT**

NAME OF DRUG: Adderall XR

NAME OF DRUG COMPANY: Shire Laboratories

INDICATION OF DRUG: Adult ADHD

DESIRED COMPLETION DATE: 6-8 weeks (NDA action date is 10/18/03)

REASON FOR REQUEST

We have an NDA supplement in for Adderall XR for adults. A preliminary look at AERS Datamart suggests that there are several cases of MI, seizures, and CVAs reported in adults. We request a search of AERS for any adverse events occurring in adults, but with a focus on serious events such as MI, seizure, CVA, and death.

Please search for both Adderall (immediate release) and Adderall XR. It would be helpful when presenting the findings to stratify the events by the formulation because there may be some relationship between the speed of release of the medication and the occurrence of the adverse events.

Please also request drug usage data for the two formulations so that we can calculate reporting rates. We will need the use broken out for adults (18-34, 35-54, 55+), since that is the population of interest.

Please contact me with any questions.

SIGNATURE OF REQUESTER Judy Racoosin, MD, MPH 4-5505	**METHOD OF DELIVERY (CHECK ONE)** □ **MAIL** □ **HAND**
SIGNATURE OF RECEIVER	**SIGNATURE OF DELIVERER**

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/s/

Russell Katz
6/24/03 08:12:27 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

MAY 8 2003

Debra J. Kelsh, M.D.
Vince & Associates Clinical Research
6600 College Blvd., Suite 330
Overland Park, Kansas 66211

Dear Dr. Kelsh:

Between April 21 and 23, 2003, Mr. Carl J. Montgomery, representing the Food and Drug Administration (FDA), conducted an investigation and met with you to review your conduct of a clinical investigation (protocol SLI 381-303 entitled " a randomized, double-blind, placebo-controlled, parallel-group study of Adderall XR in adults with attention deficit hyperactivity disorder") of the investigational drug Adderall XR (extended- release capsule of mixed salts of a single-entity amphetamine product), performed for Shire Pharmaceutical Development, Inc. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to monitor the conduct of research and to ensure that the rights, safety, and welfare of the human subjects of those studies have been protected.

From our evaluation of the establishment inspection report and the documents submitted with that report, we conclude that you adhered to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations and the protection of human subjects.

We appreciate the cooperation shown Investigator Montgomery during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely yours,

Antoine El-Hage

Antoine El-Hage, Ph.D.
Associate Director
Good Clinical Practice Branch I & II, HFD-46/47
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place, Room 125
Rockville, MD 20855

FEI: 3003955659
Field Classification: NAI
Headquarters Classification:
__X__1)NAI
_____2)VAI- no response required
_____3)VAI- response requested
_____4)OAI

cc:
HFA-224
HFD-120 Doc.Rm. NDA 21-303/SE5-005
HFD-120 Review Div.Dir. Katz
HFD-120 MO Mannheim
HFD-120 PM Homnnay-Weikel
HFD-47 c/r/s GCP File #10890
HFD-47 MO Khin
HFD-47 CSO Friend
HFR-SW350 DIB Woleske
HFR-SW350 BIMO/Investigator Montgomery
GCF-1 Seth Ray

r/d:NK:5/6/03
reviewed:AEH:5/6/03
f/t:ml:5/7/03

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Reviewer Note to Rev. Div. M.O.

- At this site, a total of 21 subjects were randomized; 18 subjects completed the study and three subjects discontinued from the study. Subject 112-008 assigned to placebo withdrew consent; subject 112-005 from Adderall XR 20mg group was discontinued due to protocol violation, particularly, alcohol abuse and subject 112-025 from Adderall XR 40mg group was discontinued due to lack of efficacy.
- An audit of all subjects' records was conducted. No FDA-483 was issued. No major compliance issue noted.
- Data appear acceptable.

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/s/

Antoine El-Hage
5/12/03 11:59:23 AM

MEMORANDUM OF TELECON

DATE: February 10, 2003

APPLICATION NUMBER: NDA 21-303/S-005, Adderall XR Capsules

BETWEEN:

Name: Debra Aleknavage, RAC, Regulatory Affairs
Phone: (240) 453-6446
Representing: Shire Pharmaceuticals

AND

Name: Anna Marie H. Weikel, Regulatory Project Manager
Division of Neuropharmacological Drug Products, HFD-120

SUBJECT: 45-day filing meeting/no filing issues identified

Background: A traditional 45-day filing meeting was held with the review team on February 10, 2003, to discuss this supplement (official filing date was February 18, 2003). The review team agreed that it was fileable and no additional issues were identified.

Discussion with Firm: Immediately after the filing meeting, I telephoned the firm and told them that their supplement will be filed and that no filing issues have been identified.

_____

Anna Marie H. Weikel
Regulatory Project Manager

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/s/

Anna-Marie Homonnay
3/11/03 04:28:26 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-303/S-005

PRIOR APPROVAL SUPPLEMENT

Shire Pharmaceutical Development Inc.
Attention: Debra Aleknavage
1801 Research Boulevard, Suite 600
Rockville, MD 20850

Dear Ms. Aleknavage:

We have received your supplemental drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Adderall XR® (mixed salts of single-entity amphetamine) Capsules

Supplement Number: NDA 21-303/S-005

Review Priority Classification: Standard (S)

Date of Supplement: December 18, 2002

Date of Receipt: December 19, 2002

These supplements provide for the treatment of Attention Deficity Disorder in adults as a new indication.

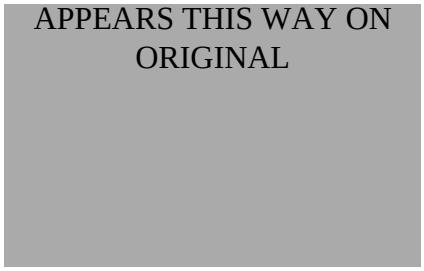
Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on February 19, 2002 in accordance with 21 CFR 314.101(a). If the application is filed, the primary user fee goal date will be October 19, 2003.

If you should have any questions, please call Ms. Anna Marie H. Weikel, R.Ph., Regulatory Project Manager, at (301) 594-5535.

Sincerely,

{See appended electronic signature page}

Robbin Nighswander, R.Ph.
Chief, Project Management Staff
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research


APPEARS THIS WAY ON
ORIGINAL

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/s/

Anna-Marie Homonnay
1/6/03 02:02:27 PM