MEMORANDUM

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

ODS PID# D040761

DATE: January 5, 2006

FROM: Kathleen M. Phelan, R. Ph., Safety Evaluator
Division of Drug Risk Evaluation

THROUGH: Rosemary Johann-Liang, M.D., Deputy Director
for Mark Avigan, M.D., C.M., Director
Division of Drug Risk Evaluation
Office of Drug Safety (ODS)

TO: M. Dianne Murphy, M.D.
Director, Office of Pediatric Therapeutics (OPT), OIASI
Office of the Commissioner
and
Solomon Iyasu, M.D., M.P.H., Acting Deputy Director
Division of Pediatric Drug Development
Office of Counter-Terrorism and Pediatric Drug Development (OCTAP)

SUBJECT: One Year Post-Pediatric Exclusivity Postmarketing Adverse Event Review
Drug : Adderall XR (dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, amphetamine sulfate)
NDA: N 21-303
Pediatric Exclusivity Approval Date : October 28, 2004

Executive Summary

The Office of Drug Safety (ODS) has been actively examining the adverse events associated with drugs used to treat attention deficit hyperactivity disorder (ADHD). Recent activities focus on cardiovascular and psychiatric adverse events as follows:

- April 27, 2004. A review of the FDA's Adverse Event Reporting System (AERS) data for marketed safety experience during stimulant therapy: death, sudden death, and cardiovascular serious adverse events (including stroke) was completed by K. Gelperin, S. Benoit, and C. Pamer.[1] ODS is exploring study methods and the suitability of available databases to objectively examine the cardiovascular effects of drugs used to treat ADHD.
- June 14, 2005. Reviews of AERS reports associated with Concerta and other methylphenidate products during the first year since granting of pediatric

[1] Gelperin, Benoit, and Pamer. April 27, 2004. PID# D030403.

exclusivity for Concerta was completed by K. Phelan.[2] This review reinforced the need to examine cardiovascular effects of drugs used to treat ADHD and also illuminated neuropsychiatric adverse events as an area needing further examination.

- September 2005. Reviews of psychiatric adverse events in each manufacturer's clinical trial and postmarketing data and in AERS was undertaken by ODS for the drugs approved by FDA to treat ADHD. The goal of the review is to characterize the psychiatric adverse events and to identify risk factors for these events if possible.
- January 2006. This review of AERS reports associated with Adderall XR during the first year since pediatric exclusivity was granted was completed by K. Phelan. Again, cardiovascular and neuropsychiatric adverse events emerge as areas of possible concern. In addition, serious adverse dermatological events associated with Adderall XR arises as a possible concern.
- February 2006. Proposals for the epidemiological study of cardiovascular adverse events associated with drugs used to treat ADHD will be discussed at the Drug Safety and Risk Management (DSaRM) Advisory Committee meeting.
- March 2006. This Adderall XR review and the results of the extensive review of psychiatric adverse events that was undertaken by ODS in September 2005 will be presented to the Pediatric Advisory Committee.

Adderall XR was granted pediatric exclusivity on October 28, 2004. This review covers Adderall XR and not immediate-release Adderall. The pediatric exclusivity 1-year reviews of Concerta and other methylphenidate products[3] did not find qualitative differences in adverse effects of immediate-release products compared to extended release products and no differences are expected with Adderall compared to Adderall XR. The more extensive reviews by ODS of the psychiatric and cardiovascular effects of drugs approved to treat ADHD will include all amphetamine and methylphenidate formulations used to treat ADHD.

A search of AERS for adverse events reported in pediatric patients during the first year after pediatric exclusivity was granted for Adderall XR found 45 unique cases. Review of these cases found three areas of current concern. These are cardiovascular, psychiatric, and dermatological adverse events. AERS reports of cardiovascular adverse events associated with stimulant medications, including Adderall XR, were reviewed by ODS in April 2004 at the request of Division of Neuropsychiatric Drug Products.[4] A warning about using Adderall XR in patients with pre-existing structural cardiac abnormalities was added to labeling. However, a controlled study could provide more definitive information than do spontaneously reported cases and ODS is pursuing avenues to perform such a study. Psychiatric adverse events arose as an area of concern in the pediatric-exclusivity 1-year review of methylphenidate products that was presented

[2] Phelan. June 14, 2005. PID# D040058 and PID# D050249.
[3] ibid.
[4] Gelperin, Benoit, and Pamer. April 27, 2004. PID# D030403.

at the June 2005 Pediatric Advisory Committee meeting.[5] As a result, a review of AERS and manufacturer data on psychiatric adverse events reported with drugs used to treat ADHD is currently being performed by ODS. The final area of concern that was found in this review, serious adverse skin reactions with Adderall XR, is not currently being addressed. This review found one well-described case of toxic epidermal necrolysis in a child in whom no other medication use was reported. A second case reported skin "peeling in sheets" in a child receiving only Adderall XR. I recommend that [redacted]

[redacted]

AERS Search Results: Adderall XR

AERS Search includes all sources - U.S. & foreign

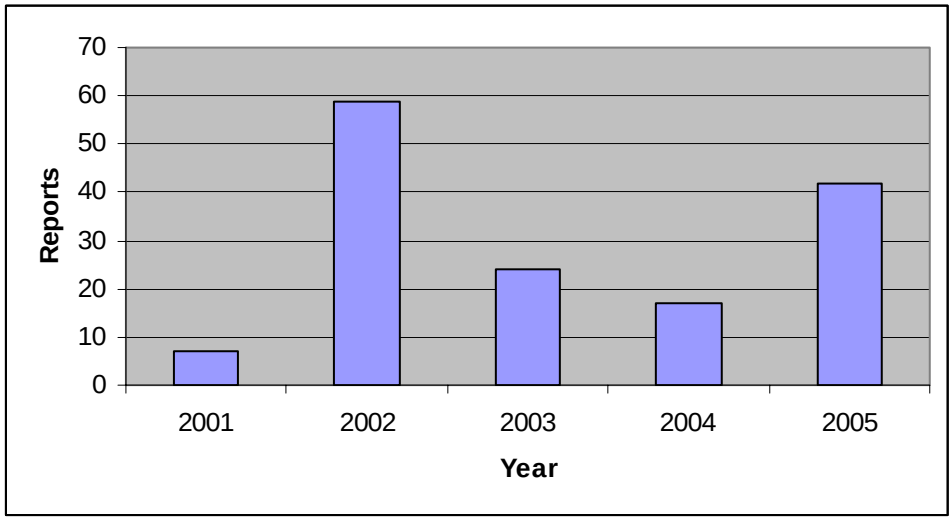
A. From marketing approval date (October 11, 2001) through AERS data cut-off date (November 28, 2005).

1. Raw counts of reports: Table 1 (parentheses denote U.S. origin report counts)

	All reports (US)	Serious(US)	Death(US)
All ages*	329 (320)	261 (252)	20 (20)
Adults (≥17)	113 (110)	99 (96)	11 (11)
Peds (0-16)	149 (143)	129 (123)	9 (9)

*Includes 67 reports with no age reported

Figure 1: Reporting trend for pediatric reports from approval date (bar graph of annual counts of reports):



[5] Phelan. June 14, 2005. PID# D040058 and PID# D050249.

2. Counts of top 20 reported event preferred terms for all ages, adults, and pediatric age groups. Underlined events are not described in the label.

All ages: pharmaceutical product complaint (66), drug ineffective (41), abnormal behaviour (26), psychotic disorder (21), aggression (18), convulsion (18), drug effect decreased (17), agitation (16), medication error (15), insomnia (14), disturbance in attention (13), headache (13), vomiting (13), chest pain (11), nausea (11), abdominal pain upper (10), depression (10), dizziness (10), fatigue (10), hypertension (10)

Adults: psychotic disorder (12), pharmaceutical product complaint (11), drug ineffective (10), fatigue (8), nausea (8), abnormal behaviour (7), agitation (7), cardiac arrest (7), depression (7), insomnia (7), medication error (7), anxiety (6), cardiomyopathy (6), tremor (6), chest pain (5), convulsion (5), drug abuser (5), drug screen positive (5), hypertension (5), paranoia (5)

Peds: pharmaceutical product complaint (25), abnormal behaviour (16), drug ineffective (16), aggression (12), convulsion (11), drug effect decreased (9), abdominal pain (8), irritability (8), disturbance in attention (7), headache (7), insomnia (7), vomiting (7), abdominal pain upper (6), agitation (6), arrhythmia (6),educational problem (6), psychotic disorder (6), chest pain (5), attention deficit/hyperactivity disorder (4), circulatory collapse (4)

B. From Pediatric Exclusivity approval date (October 28, 2004) through AERS data cut-off date (November 28, 2005):

1. Raw counts of reports: Table 2 (parentheses denote U.S. origin report counts)

	All reports (US)	Serious (US)	Death (US)
All ages*	210 (204)	177 (171)	15 (15)
Adults (≥17)	72 (69)	65 (62)	5 (5)
Peds (0-16)	98 (97)	90 (89)	8 (8)

*Includes 40 reports with no age reported

2. Counts of top 20 reported event preferred terms for all ages, adults, and pediatric age groups. Underlined events are not described in the label.

All ages: pharmaceutical product complaint (35), drug ineffective (26), abnormal behaviour (16), headache (13), agitation (12), therapeutic response unexpected with drug substitution (12), anxiety (10), drug effect decreased (10), heart rate increased (10), loss of consciousness (10), aggression (9), blood pressure increased (9), chest pain (9), fatigue (9), insomnia (9), psychotic disorder (9), weight decreased (9), depression (8), prescribed overdose (8), suicidal ideation (8)

Adults: anxiety (8), fatigue (8), abnormal behaviour (7), depression (6), pharmaceutical product complaint (6), agitation (5), drug abuser (5), headache (5), prescribed overdose (5), pyrexia (5), tachycardia (5), delusion (4), drug ineffective (4),

influenza (4), insomnia (4), nausea (4), nephrolithiasis (4), pain (4), paranoia (4), psychotic disorder (4)

Peds: pharmaceutical product complaint (13), drug ineffective (10), heart rate increased (9), abnormal behaviour (8), chest pain (7), headache (7), loss of consciousness (7), aggression (6), blood pressure increased (6), irritability (6), weight decreased (6), anorexia (5), drug effect decreased (5), insomnia (5), psychotic disorder (5), sudden cardiac death (5), feeling abnormal (4), glaucoma (4), pallor (4), palpitations (4)

Hands-on review of all pediatric adverse event reports from all sources received during the one-year after Adderall XR received pediatric market exclusivity.

Of 98 reports retrieved by this search, 4 involve adults, 29 involve immediate-release Adderall or the formulation was unclear, 16 are duplicates, and 4 report no adverse effects (see Attachment 2). The remaining 45 cases reporting adverse events associated with Adderall XR in patients aged 0 to 16 years are described below (also see Attachment 1).

A. General characteristics of reports

Gender: 11 female, 34 male

Standard AERS age breakdown:

0-<1 mo	0
1 mo.- <2 yrs	0
2-5 yrs	2
6-11 yrs	33
12-16 yrs	10

Outcomes selected on MedWatch form[6]: 4[7] deaths, 13 hospitalizations, 8 life threatening, 2 disabling, 6 requiring intervention, 26 other, 2 no outcome selected.

Indications or clinical conditions for which the drug was used: 32 attention deficit/hyperactivity disorder (ADHD), 1 learning disability, 12 unknown.

Doses: range 5 to 110 mg/day; mean (omitting single 110 mg value) 17 mg/day; median 15 mg/day.

[6] A report may have more than one outcome selected.
[7] Three reports had the death checkbox selected but a fourth case reported death in the narrative.

B. Comments on labeling status of the top 20 adverse events in pediatric patients and comparison to adult adverse event profile.

The unlabeled pediatric adverse events are pharmaceutical product complaint, abnormal behavior, loss of consciousness, aggression, feeling abnormal, glaucoma, and pallor. These are analyzed in the following section.

Although sudden death and myocardial infarction are in Adderall XR labeling in the Adverse Reactions section, reports of death in patients being treated for a non-life-threatening illness are always of concern. The Office of Drug Safety is exploring epidemiological approaches to evaluating the cardiovascular effects of drugs used to treat ADHD using available databases. Study design will be discussed in February 2006 at a meeting of the Drug Safety and Risk Management Advisory Committee.

The top 20 adult adverse event profile differs from the pediatric adverse event profile in having more specific psychiatric adverse events listed, including paranoia and delusion. Both adult and pediatric profiles include psychotic disorder, however. More misuse is reflected in the adult profile, including prescribed overdose, and drug abuser. This may be as expected because the adult population has greater control over their own drug use than do children. Finally, the adult profile shows more physical ailment that does not follow from the known pharmacology of amphetamines, including influenza and nephrolithiasis. These events may reflect the health of the adult population rather than direct drug effects. Thus, a comparison of the adult and pediatric top 20 adverse events for the pediatric exclusivity 1-year review period does not indicate different effects of Adderall XR in pediatric and adult patients.

C. Comments and analysis of unlabeled adverse events seen in pediatric population.

The unlabeled pediatric adverse events in the top 20 events are pharmaceutical product complaint, abnormal behavior, loss of consciousness, aggression, feeling abnormal, glaucoma, and pallor. Review of the cases reported in the 1-year exclusivity period reduced the number of glaucoma cases to one. Adderall XR labeling contraindicates use in patients with glaucoma but glaucoma is not listed in the Adverse Events section. In the AERS case, glaucoma in one eye is suspected during Adderall XR use and glaucoma in both eyes is suspected after Adderall XR has been switched to OROS methylphenidate. Thus, glaucoma is not diagnosed definitively and there is no real dechallenge information to help evaluate causality. Pharmaceutical product complaint, abnormal behavior and feeling abnormal are general descriptions which can encompass a number of adverse events and, thus, are not specific enough to merit labeling. Similarly, pallor and loss of consciousness, although specific, describe symptoms and are not the primary adverse events in the cases in which they are reported. Thus, based on these cases, pallor and loss of consciousness should not be labeled outside of the context of the primary adverse events with which they have been associated. The remaining unlabeled adverse event

reported most frequently in pediatric patients taking Adderall XR is aggression. Because of concerns about the psychiatric adverse events reported with ADHD drug treatments, FDA is currently evaluating aggression and other psychiatric events with these drugs to determine appropriate action.

Two unlabeled adverse events in the reviewed cases, but not in the top 20 reported events, that were investigated in more detail are serious skin rashes and asthma. Toxic epidermal necrolysis (TEN) was reported in a detailed case in a 10-year-old male after 4 days treatment with Adderall XR (ISR# 4653131). TEN required 2 weeks of intensive care and a total of 3 weeks hospitalization. Over the course of the event, the patient developed acute renal failure and airway edema with intubation. No concomitant drugs are listed, although prior ADHD treatment and treatment of the adverse event are described, suggesting that if there had been concomitant drug use, it too would have been described. The patient had a history of rash with amoxicillin. A second, less detailed case of generalized rash with "skin peeling in sheets" was reported in a 9-year-old male after 5 months Adderall XR treatment of ADHD (ISR# 4681638). The patient had a history of eczema at birth but no concurrent medical conditions. He received no concomitant medications. An AERS search of the Skin and Subcutaneous Tissue Disorders SOC for Adderall XR in patients aged 0 to 16 years found 3 reports each of Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN). Hands-on review of the reports is necessary to determine the number of unique cases and whether there is any evidence of association with Adderall XR. Because TEN and SJS are life-threatening and drug hypersensitivity is a known cause of these severe rashes, even a few cases are important.

New-onset asthma was reported in a 14-year-old female temporal to Adderall XR treatment for an unspecified indication (ISR# 4539062). The patient experienced shallow cough and tickle in the throat after the first Adderall XR dose. After the second or third dose, she experienced her first asthma attack. Adderall XR was discontinued and asthma was treated with fluticasone propionate. Fluticasone was discontinued after about 3 months when asthma symptoms had ceased. A couple weeks later, the patient responded to one dose of Adderall XR with shallow cough and tickling in the throat. Although adverse respiratory effects are not expected with amphetamines, the positive rechallenge in this case is suggestive of an association. In another case, respiratory arrest is reported in a 7-year-old male after 1 to 2 weeks Adderall XR treatment of ADHD (ISR# 4681972). The patient had pre-existing "severe" asthma and the respiratory arrest, which occurred after physical exertion, was attributed to asthma. An AERS search of the Respiratory, Thoracic, and Mediastinal Disorders SOC for Adderall XR in patients aged 0 to 17 years found reports of dyspnea (4), respiratory arrest (2), and one report each of asthma, respiratory distress, stridor, and wheezing. Thus, no additional reports of asthma were found and this small number of respiratory adverse events does not suggest a serious problem with Adderall XR at this time.

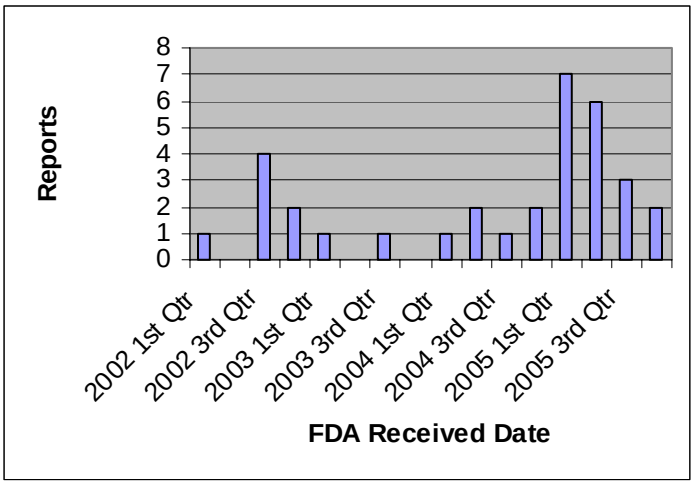
D. Comments and analysis of labeled events that are uniquely reported in pediatric patients but are not reported in the adult population.

Chest pain, loss of consciousness, aggression, blood pressure increased, irritability, weight decreased, anorexia, sudden cardiac death, feeling abnormal, glaucoma, pallor, and palpitations appear in the pediatric top 20 adverse events for the 1-year exclusivity review period but not in the adult top 20 adverse events. However, the adult profile includes tachycardia, and the top 20 adverse events reported in adults since Adderall XR approval include cardiac arrest, hypertension, chest pain, and cardiomyopathy. Thus, the cardiac profile in adults and children appears to be qualitatively similar. The psychiatric profile in children may reflect less self-regulation in that children act on feelings more frequently than adults resulting in reports of aggression and irritability. Whether this is the case or whether there is a difference in the psychiatric effects of Adderall XR in children and adults cannot be determined using postmarketing adverse event reports.

E. Comments on increased reporting frequency of expected events.

The labeled adverse events with increased reporting frequency in the 1-year review period compared to the reporting frequency since Adderall XR approval are cardiovascular and nutritional. The adverse events are heart rate increased, blood pressure increased, sudden cardiac death, palpitations, weight decreased, and anorexia. The increased reporting of cardiovascular adverse events may reflect stimulated reporting in response to publicity surrounding the Adderall removal and return to market in Canada. Canada removed Adderall and Adderall XR from the market in February 2005 and returned them to the market in August 2005. Figure 2, below, shows when FDA received the 33 reports in the Cardiac Disorders SOC in patients aged 0 to 17 years. Figure 2 illustrates the highest reporting in the first and second quarters of 2005, corresponding to the removal of Adderall and Adderall XR from the Canadian market.

Figure 2: Numbers of cardiac disorders reports in patients aged 0 through 16 years received by the FDA per quarter.



The increased reporting of anorexia and weight loss is less easily explained as these adverse events are well-known and labeled.

F. Reports of death.

The AERS search retrieved eight reports with the outcome of death selected on the MedWatch form during the 1-year period following the granting of pediatric exclusivity for Adderall XR. Two were duplicate reports, one involved an adult patient, and two involved immediate-release Adderall, leaving three cases reporting death. A fourth case reporting death was found during hands-on review of the pediatric cases received during the 1-year review period. The four deaths in pediatric patients appear to be cardiovascular events and are summarized below. One death occurred in a patient who was found on autopsy to have cardiovascular anomalies, one report contains very little information, one death occurred after the first dose of Adderall XR during physical exertion in a patient with a family history of cardiac arrhythmia, and one death occurred 2 months after Adderall XR was discontinued.

ISR# 4644584, direct report, U.S.
A 10-year-old boy collapsed at home after 22 months treatment of ADHD with Adderall XR 15 mg/day. There were no concomitant medications. "Agonal cardiac rhythm and narrow complex rhythm" were obtained during transport to the hospital. The patient was asystolic upon arrival at the ER. Autopsy found coronary artery anomalies consisting of an acute angle in the outflow tract of the right coronary artery and reduplication of the left coronary artery. Subsequent evaluation of other family members found short QT syndrome.

ISR# 4627211, 15-day report, U.S.
A 10 year-old male experienced sudden death while taking Adderall XR. Indication, dosage, duration of use, medical history, concomitant medications, cause of death are all unknown.

ISR# 4708999, 15-day report, U.S.
A 12-year-old male who took methylphenidate for 4 years to treat ADHD was switched to Adderall XR 10 mg/day. On the day he took his first dose of Adderall XR, he collapsed and died after running one to two miles cross-country. His death certificate reported sudden cardiac death. Autopsy found no abnormalities. The patient's mother had been treated for ventricular tachycardia by implanted defibrillation and, 2 years later, ablation.

ISR# 4599589, 15-day report, U.S.
An 11-year-old male took Adderall XR, 15 mg/day, to treat ADHD from April 29, 2004 until an unspecified date in August 2004. On [redacted] he was found unresponsive and could not be revived. Autopsy listed the cause of death as

cardiopulmonary arrest of obscure causes. At the time of death, the patient was taking atomoxetine and bupropion.

G. Summary of the pediatric adverse event profile for events such as maternal exposure, overdose, or multiple drug usage.

There were no reports of maternal exposure in the 1-year review period.

Four cases report overdose including three cases reporting prescribed doses greater than the maximum recommended pediatric dose of 30 mg/day. A 13-year-old female experienced insomnia and shingles after 3 years treatment of ADHD with 110 mg/day Adderall XR. She was also receiving venlafaxine. A 10-year-old male who was taking 40 mg/day Adderall XR to treat ADHD took a single 740 mg dose in a suicide attempt. The reported adverse events were psychosis, agitation, and insomnia, but the suicide attempt itself may be assessed as a possible adverse event. A 10-year-old male experienced suspected glaucoma in one eye after approximately 2 years Adderall XR to treat ADHD. Adderall XR dosage was 40 mg/day for an unspecified duration. A 10-year-old female who received 15 mg/day Adderall XR became violent and disruptive in school. The paramedic who was called said that she was experiencing a drug overdose.

Reported concomitant drugs are atomoxetine (2), bupropion, ibuprofen, mirtazapine, sertraline, topiramate, loratidine, lorazepam, paroxetine, insulin, citalopram, risperidone, salbutamol, fluticasone, salmeterol, montelukast, azithromycin, venlafaxine, midodrine, lansoprazole, Bactrim, fludrocortisone, and valproic acid. There is no particular pattern of concomitant drug use to suggest a specific drug as a contributing factor to the adverse events; although, an interaction is not ruled out by these data. An additional report included grape juice and described the juice as the only variable in the child's usual habits on the day he experienced loss of consciousness and "extremely high" amphetamine levels were measured. The physician associated the grape juice with possibly accelerated amphetamine release from Adderall XR.

Summary

Adderall XR was granted pediatric exclusivity on October 28, 2004. A search of AERS for adverse events reported in pediatric patients during the first year after pediatric exclusivity was granted for Adderall XR found 45 unique cases. Review of these cases found three areas of current concern. These are cardiovascular, psychiatric, and dermatological adverse events. AERS reports of cardiovascular adverse events associated with stimulant medications, including Adderall XR, were reviewed by ODS in April 2004 at the request of Division of Neuropsychiatric Drug Products.[8] A warning about using Adderall XR in patients with pre-existing structural cardiac abnormalities

[8] Gelperin, Benoit, and Pamer. April 27, 2004. PID# D030403.

was added to labeling. However, a controlled study could provide more definitive information than do spontaneously reported cases and ODS is pursuing avenues to perform such a study. Psychiatric adverse events arose as an area of concern in the pediatric-exclusivity 1-year review of methylphenidate products that was presented at the June 2005 Pediatric Advisory Committee meeting.[9] As a result, a review of AERS and manufacturer data on psychiatric adverse events reported with drugs used to treat ADHD is currently being performed by ODS. The final area of concern that was found in this review, serious adverse skin reactions with Adderall XR, is not currently being addressed. I recommend

signed December 30, 2005
Kathleen M. Phelan, R.Ph.
Safety Evaluator

Concur:

signed December 30,2005
Cindy Kortepeter, Pharm. D.
Safety Evaluator Team Leader

Limitations of the Adverse Event Reporting System (AERS)

AERS collects reports of adverse events from health care professionals and consumers submitted to the product manufacturers or directly to the FDA. The main utility of a spontaneous reporting system, such as AERS, is to identify potential drug safety issues. There are inherent limitations to the voluntary or spontaneous reporting system, such as underreporting and duplicate reporting; for any given report, there is no certainty that the reported suspect product(s) caused the reported adverse event(s); and raw counts from AERS cannot be used to calculate incidence rates or estimates of drug risk for a particular product or used for comparing risk between products.

Attachments

1. Adverse event cases with Adderall XR (N=45)
2. Cases that reported no adverse event (N=4)

[9] Phelan. June 14, 2005. PID# D040058 and PID# D050249.

Attachment 1: Adverse event cases with Adderall XR (N=45)

Cardiovascular Adverse Events (N=14)			
ISR#	**Age (yrs)**	**Gender**	**Summary**
4525970	6	Male	Open heart surgery for unspecified cardiac "issue" after turning blue and losing consciousness after 2.5 years Adderall XR. History of heart murmur.
4591018	5	Male	Tachycardia of 150 bpm, palpitations, and chest pain during treatment with Adderall XR for ADHD. Atomoxetine concomitant. Drugs and events continue.
4589267	7	Female	Prolonged QTc interval and sinus tachycardia after 1 month Adderall XR to treat ADHD. Prolonged QTc resolved with dosage reduction.
4582466	7	Male	Rapid heart rate and increased impulsivity 6 months after start Adderall XR to treat ADHD. Drug and events continue.
4666488	7	Male	Cardiac disorder ("blocked blunder of left vessel") less than 1 month after Adderall XR of 2-months duration was switched to immediate-release Adderall. Event continued after Adderall discontinuation.
4779440	9	Male	Chest pain, cyanosis, sweating, and loss of consciousness after 3 years Adderall XR to treat ADHD. ECG results unknown. Events resolved with Adderall XR discontinuation. No concomitant drugs.
4644584	10	Male	Cardiac arrhythmia and death after 22 months Adderall XR treatment for ADHD. Coronary artery anomalies per autopsy. Family history of short QT syndrome.
4627211	10	Male	Sudden death during use of Adderall XR. No other information provided.
4648923	11	Male	Supraventricular tachycardia after 18 months Adderall XR to treat ADHD. Event resolved in ER and Adderall XR was discontinued. Concomitant ibuprofen. Maternal history of heart murmur.
4599589 also 4638248	11	Male	Cardiopulmonary arrest and death 2 months after Adderall XR ADHD treatment of 4 months duration was discontinued. Concomitant atomoxetine and bupropion.
4603756	14	Female	Chest pain, palpitations, tachycardia to 150 bpm, anorexia, weight loss during 3 months Adderall XR to treat a learning disability. Adderall XR and events continue. Concomitant mirtazapine for sleep, sertraline for depression, topiramate for unspecified indication. History of anorexia/bulemia and suicide attempt with cardiac arrest.

ISR#	Age (yrs)	Gender	Summary
4803868	16	Male	Chest pain during an athletic event and inverted T wave on ECG after 7 months Adderall XR to treat ADHD. Chest pain resolved. Adderall XR was discontinued and ECG abnormality continued. Concomitant loratidine.
4708999	12	Male	Sudden cardiac death on day of first Adderall XR dose after running one to two miles. Had taken methylphenidate for 4 years before switch to Adderall XR to treat ADHD. Maternal history of ventricular tachycardia treated with implanted defibrillation and then ablation.
4616311	14	Female	Episode of autonomic dysfunction occurred after 1 month Adderall XR. Periods of unconsciousness began occurring after 11 months Adderall XR to treat ADHD. Echocardiogram showed aortic regurgitation, tilt table test showed vasovagal syncope, stress test showed orthostatic hypotension. Autonomic dysfunction and Adderall XR continue. Concomitant midodrine for orthostatic hypotension, lansoprazole for acid reflux, Bactrim for acne, fludrocortisone for unspecified indication. History of exercise-induced asthma.
Psychiatric Adverse Events (N=15)			
ISR#	**Age (yrs)**	**Gender**	**Summary**
4750189	3	Male	Visual hallucinations within 1 day of starting Adderall XR to treat ADHD. Events continue with switch to dextroamphetamine. No concomitant drugs.
4786843	6	Male	Visual and auditory hallucinations, paranoia, insomnia, and homicidal ideation after one dose Adderall XR. Events resolved with switch to dexmethylphenidate. No concomitant drugs.
4707208	7	Female	Aggression, agitation, hostility, irritability during 5 weeks of Adderall XR to treat ADHD. Adderall XR discontinued. Diagnosed with bipolar disorder, started on lithium and risperidone. Events continue.
4687389	7	Male	Psychotic episode and physical assault, per mother, after one dose of lorazepam during use of Adderall XR. Outcome unknown.
4502929	7	Male	Crying, moodiness, irritability during 2 weeks of Adderall XR to treat ADHD. Events continued after switch to methylphenidate.

ISR#	Age (yrs)	Gender	Summary
4707275	8	Female	Increased aggression and fits of rage developed over 2 year period of methylphenidate (1 year) and Adderall XR (about 1 year) treatment of ADHD. Adderall XR and events continue.
4673111	8	Male	Tic, psychosis, logorrhea, musculoskeletal stiffness, crying, bone pain, akathisia, high blood pressure, increased heart rate, and insomnia within 1 hour of first dose of Adderall XR to treat ADHD. During hospitalization, right atrial enlargement was found by ECG. Events resolved with hospitalization and Adderall XR discontinuation. Atrial enlargement resolved at an unspecified time. History of mood disorder.
4754329	9	Female	Suicidal ideation and behavior, irritability, and "discomfort" within 5 days of starting Adderall XR to treat ADHD. Events resolved with Adderall XR discontinuation. Concomitant paroxetine for anxiety disorder. History of juvenile diabetes treated with insulin pump.
4589221	10	Female	Violent behavior, feeling hot, amnesia after 2.5 weeks Adderall XR to treat ADHD. Events resolved with Adderall XR discontinuation.
4616251	10	Male	Suicide attempt by overdose on Adderall XR resulting in psychosis, agitation, insomnia, during Adderall XR treatment of unknown duration for ADHD.
4712970	10	Male	Product complaint. Palpitations, nightmares, night terrors, drugged appearance during use of one bottle of Adderall XR but not during use of other bottle. + de- and re-challenges.
4726064	11	Male	Depression, psychosis, suicidal and homicidal ideation after 2 years Adderall XR to treat ADHD. Mania occurred with antidepressant treatment. Patient diagnosed with bipolar disorder. Adderall XR replaced with treatment for bipolar.
4586854	14	Male	Paranoia, irrationality, confusion, agitation and high amphetamine urine concentration 40 hours after last Adderall XR dose. Patient denied taking additional drug and parent says pill count supports this. Patient had been taking Adderall XR for 2 years to treat ADHD. Concomitant citalopram and risperidone for OCD.
4631143	12	Male	Visual and auditory hallucinations, suicide attempts during Adderall XR of 4 months duration to treat ADHD. Events resolved with Adderall XR discontinuation.
4492777	13	Female	Insomnia and shingles after 3 years Adderall XR 110 mg/day to treat ADHD. Shingles resolved with treatment. Insomnia and Adderall XR continue. Concomitant venlafaxine for depression and anxiety.

Neurological Adverse Events (N=5)			
ISR#	**Age (yrs)**	**Gender**	**Summary**
4505420	6	Female	Trance-like mental state and dyskinesia 2 hours after first Adderall XR dose to treat ADHD. Events resolved with discontinuation. No concomitant drugs.
4681636	6	Female	Seizure during treatment with Adderall XR. History of heart murmur and seizure disorder. Adderall XR continued.
4834420	11	Male	Orofacial dyskinesia after about 4 months Adderall XR to treat ADHD. Event resolved with Adderall XR discontinuation. Concomitant drugs salbutamol, fluticasone, salmeterol, and montelukast to treat asthma and one dose azithromycin 1- 12 days (unclear) before event.
4622705	16	Male	Depressed consciousness, hallucinations, hypersalivation, respiratory arrest, tics, muscle stiffness after second Adderall XR dose to treat ADHD. Event was treated in ER, Adderall XR was discontinued, adverse events resolved.
4697690	13	Male	Lower leg spasticity and inability to walk within 1 month of starting Adderall XR to treat ADHD. Events resolved in about 3 months after Adderall XR discontinuation. Methylphenidate and gabapentin were started 1 month after Adderall XR was discontinued.
Respiratory Adverse Events (N=3)			
ISR#	**Age (yrs)**	**Gender**	**Summary**
4681972	7	Male	Respiratory arrest followed by cardiac arrest after physical exertion 1 week after starting Adderall XR to treat ADHD. After defibrillation and hospitalization, patient recovered and was switched to methylphenidate. History of severe asthma.
4653369	10	Male	Dyspnea, throat tightness, visual disturbance after first dose of Adderall XR. Events resolved with diphenhydramine.
4539062	14	Female	Cough and tickle in throat after first Adderall XR dose, new onset asthma after third Adderall XR dose. Adderall XR was discontinued, event was treated with fluticasone propionate and resolved over 3 months. Single-dose Adderall XR rechallenge 1 month after asthma resolved was followed by recurrence of cough and tickle in throat.

Dermatological Adverse Events (N=2)			
ISR#	**Age (yrs)**	**Gender**	**Summary**
4681638	9	Male	Generalized rash and skin exfoliation after 5 months Adderall XR to treat ADHD. Adderall XR discontinued, fever and bacterial infection developed. After IV antibiotics and hospitalization, events resolved. History of eczema.
4653131	10	Male	TEN, acute renal insufficiency, encephalopathy, airway edema after 5 days Adderall XR to treat ADHD. Events resolved with hospital intensive care and Adderall XR discontinuation.
Growth and Nutritional Adverse Events (N=3)			
ISR#	**Age (yrs)**	**Gender**	**Summary**
4804830	9	Male	Growth suppression during Adderall XR use of unknown duration. Adderall XR discontinued. Event ongoing.
4620153	10	Male	Weight loss, anorexia, upset stomach, headache during Adderall XR use of 4-months duration to treat ADHD. Events resolved with switch to atomoxetine.
4664213	10	Male	Weight loss, increased blood pressure, headache during use of Adderall XR. Events resolved with Adderall XR discontinuation.
Other Adverse Events (N=3)			
ISR#	**Age (yrs)**	**Gender**	**Summary**
4527322	9	Male	Increased PT and INR, palor, asthenia, weight loss, feeling cold during treatment with Adderall XR and valproic acid for ADHD and bipolar disorder. Drugs and events ongoing.
4797366	10	Male	Suspected glaucoma after about 20 months Adderall XR treatment of ADHD. Events continued with switch to methylphenidate.
4779435	11	Male	"Extremely" high amphetamine levels and loss of consciousness after Adderall XR dose was followed with grape juice. Physician attributed event to rapid release of amphetamine caused by juice. Events resolved and Adderall XR was continued.

Attachment 2: Cases that reported no adverse event (N=4)

No Adverse Event Reported			
ISR#	**Age (yrs)**	**Gender**	**Summary**
4795687	8	Male	Product complaint. Adderall XR capsules were partially filled. No adverse event occurred.
4539459	9	Male	Wrong strength Adderall XR dispensed and taken by patient. No adverse event occurred.
4711581	16	Female	Medication error. Empty Adderall XR package received from mail-order pharmacy. No adverse event occurred.
4545209	11	Male	Drug ineffective. Adderall XR ineffective in treating patient's ADHD.

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

/s/

Kathleen Phelan
1/5/2006 11:21:56 AM
DRUG SAFETY OFFICE REVIEWER

Rosemary Johann-Liang
1/9/2006 09:44:33 AM
MEDICAL OFFICER