MEMORANDUM

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

ODS PID# D060042

DATE: February 1, 2006

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

THROUGH: Rosemary Johann-Liang, M.D., Deputy Director
for Mark Avigan, M.D., C.M., Director
Division of Drug Risk Evaluation (DDRE)
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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: Adverse events reported with immediate-release mixed amphetamine salt products during the Adderall XR 1-year post-pediatric exclusivity period
Drug : Adderall (dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, amphetamine sulfate)
NDA: 11-522
Approval Date: January 19, 1960

EXECUTIVE SUMMARY

This document summarizes adverse events associated with immediate-release mixed amphetamine salts in pediatric patients that were reported to FDA during the 1-year Adderall XR post-pediatric exclusivity period from October 28, 2004 through November 28, 2005. The purpose of this review is to determine whether adverse events reported with immediate-release mixed amphetamine salts differ from those reported with Adderall XR.

Adderall XR was granted pediatric exclusivity on October 28, 2004. A search of AERS for adverse events associated with Adderall XR reported in pediatric patients during the first year after pediatric exclusivity was granted found 98 reports. Of these 98 reports, 27 were unique cases involving patients aged 0 to 16 who were taking mixed amphetamine salts of immediate-release or unknown formulation. A second AERS search that

included both Adderall and Adderall XR found three additional Adderall XR cases but no additional immediate-release mixed amphetamine salts cases. The additional cases were found because the drug list used to search AERS for this review contained more Adderall XR verbatim terms than the drug list used to search AERS for the Adderall XR review. The three additional Adderall XR cases are summarized in Attachment 2, but are not discussed in this document. These three cases comprise one death that may have been cardiac in nature and two reports of panic and anxiety. The 27 immediate-release or unknown formulation mixed amphetamine salts cases present an adverse event (AE) profile that is qualitatively similar to that of Adderall XR. As with Adderall XR[1] and methylphenidate,[2] the main categories of AEs reported in the 1-year post-pediatric exclusivity period were cardiovascular, psychiatric, and neurological. Neurological AEs are labeled; cardiovascular and psychiatric AEs are being explored further by DDRE, as described in the bullet points below. There were two deaths, both cardiac events in patients found on autopsy to have cardiac anomalies.

Mixed amphetamine salts product labels include seizure, dyskinesia, and exacerbation of tics and Tourette's syndrome. Methylphenidate labels list Tourette's syndrome as a rare AE without describing the effect as exacerbation. The Division of Drug Risk Evaluation (DDRE) will recommend to the Division of Psychiatric Products (DPP) that updating relevant stimulant labels be considered to ensure consistency in describing these events.

Also found in this review were one case each of Steven's Johnson Syndrome and suspected glaucoma. These adverse events arose as areas of possible concern in the Adderall XR pediatric 1-year review. Since the Adderall XR 1-year pediatric review, DPP has requested that DDRE review the issue of serious adverse dermatological events reported with mixed amphetamine salts. Because the 1-year pediatric reviews of both Adderall XR and immediate-release Adderall retrieved cases of suspected glaucoma, I recommend that the issue of glaucoma reported with mixed amphetamine salts be investigated further to determine if any regulatory action is warranted. The Office of Counter-Terrorism and Pediatric Drug Development (OCTAP) should send a formal consult request to the Office of Drug Safety (ODS), DDRE, if they agree with the recommendation to look specifically at the issue of glaucoma reported with mixed amphetamine salts.

Investigations into cardiovascular and psychiatric adverse events associated with drugs used to treat ADHD are currently ongoing. Specifically, the following two FDA advisory committee meetings are being convened in the near future to address these issues:

- 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.

[1] Phelan. Adderall XR one-year post-pediatric exclusivity postmarketing adverse event review. January 5, 2006. PID# D040761

[2] Phelan. Concerta one-year post-pediatric exclusivity postmarketing adverse event review and Adverse events with methylphenidate products other than Concerta in pediatric patients during the first year after granting of pediatric exclusivity for Concerta. June 14, 2005. PID# D040058 and PID# D050249.

- March 2006. The Adderall XR review, this immediate-release mixed amphetamine salts review, and the results of the extensive review of psychiatric adverse events that was undertaken by ODS since September 2005 will be presented to the Pediatric Advisory Committee.

BACKGROUND

Adderall was originally marketed in 1960 in a different formulation as an anorexiant under the trade name Obetrol. In May 1994, the currently formulated product was given the trade name Adderall and marketed by a different sponsor. Subsequently, the new sponsor became aware that Adderall was an unapproved new drug and undertook actions to gain FDA approval. In 1996, Adderall was approved to treat ADHD and narcolepsy and the obesity indication was removed from labeling.

Adderall XR was approved to treat ADHD and narcolepsy on October 11, 2001; although, current labeling includes only ADHD. On October 28, 2004, Adderall XR was granted pediatric exclusivity. A 1-year post-pediatric exclusivity postmarketing adverse event review was completed for Adderall XR by DDRE. The Adderall XR review identified psychiatric, cardiovascular, and dermatological events as areas of possible concern. DDRE is currently investigating psychiatric and cardiovascular effects of drugs approved to treat ADHD. An AERS review of serious skin adverse events associated with mixed amphetamine salts will be undertaken by DDRE, at the request of DPP.

AERS SEARCH

Search Criteria

Drug: Adderall, Adderall XR
Age range: 0 to 17 years
FDA received dates: October 28, 2004 through November 28, 2005

Search Results

The AERS search for the Adderall XR pediatric postmarketing adverse event review retrieved 98 reports using only Adderall XR and it's verbatims as search terms. Among the 98 reports which were sorted for the Adderall XR pediatric 1-year review, 29 involved immediate-release Adderall or the formulation was unclear. Review of the 29 immediate-release or unknown formulation Adderall cases found that 2 involve adults.

The AERS search performed for this document included Adderall, Adderall XR, and their verbatims and retrieved 102 reports. Comparison of the results from the two searches found three additional cases involving Adderall XR, but no additional cases involving Adderall. The additional cases were found because the drug list used to search AERS for this review contained more Adderall XR verbatim terms than the drug list used to search AERS for the Adderall XR review. The three Adderall XR cases do not change the adverse event profile, so they are not discussed in this document but are summarized in Attachment 2. These three cases comprise one death that may have been cardiac in nature and two reports of panic and anxiety. This document describes the 27 pediatric

adverse event cases associated with immediate-release or unknown-formulation mixed amphetamine salts. See Attachment 1 for brief summaries of these 27 cases.

General Characteristics Of Reports (N=27)

Gender: 6 female, 21 male

Standard AERS age breakdown:

0-<1 mo	0
1 mo.- <2 yrs	0
2-5 yrs	2
6-11 yrs	15
12-16 yrs	10

Outcomes selected on MedWatch form[3]: 2 deaths, 6 hospitalizations, 1 life threatening, 0 disabling, 2 requiring intervention, 15 other, 2 no outcome selected.

Indications or clinical conditions for which the drug was used: 13 attention deficit/hyperactivity disorder (ADHD), 8 attention deficit disorder (ADD), 6 unknown.

Dosages (N=16): range 5 to 60 mg/day; mean 28 mg/day; median 20 mg/day.

Time to onset (number of cases including information):
all cases (N=15): range less than 2 weeks to "years"; median 3 months.
cardiovascular (N=5): range 3 weeks to 2 years; median 5 months.
psychiatric (N=2): less than 2 weeks, 6 months.
neurological (N=6): less than 1 month (3), "several months" (1), about 1 year (2).
dermatological (Steven's Johnson syndrome, N=1): 3 weeks.
other (suspected glaucoma, N=1): "years".

Reports Of Death.

Of the 27 AERS cases of adverse events associated with immediate-release or unknown formulation mixed amphetamine salts reported in pediatric patients during the 1-year period following the granting of pediatric exclusivity for Adderall XR, 2 had the outcome of death. The two deaths in pediatric patients appear to be cardiovascular events and are summarized below. One patient was found on autopsy to have a "genetic cardiac problem" and the other patient was found on autopsy to have a bicuspid aortic valve.

ISR# 4648776, MFR# SUS1-2005-00234, U.S.
A 12-year-old female experienced sudden cardiac death while running after taking Adderall 30 mg/day for 5 months for an unspecified indication. Concomitant

[3] A report may have more than one outcome selected.

medication was atomoxetine 54 mg/day that "began to be titrated 3 weeks before the patient's death." The patient's pulse had been 93 bpm at her most recent office visit. Autopsy found an unspecified "genetic cardiac problem."

ISR# 4597574, Direct report, U.S.
A 7-year-old male died in his sleep 3 weeks after resuming treatment of ADHD with Adderall following a summer break from Adderall. Autopsy found a bicuspid aortic valve and the patient had a history of infantile heart murmur. Death was attributed to cardiac arrhythmia.

Summary Of The Pediatric Adverse Event Profile For Events Such As Maternal Exposure, Overdose, Or Multiple Drug Usage.

One case reported oppositional defiant disorder in a 5-year-old boy who was exposed to Adderall during the first 5 months *in utero*. The mother was taking 45 mg/day of Adderall to treat ADHD. Additional *in utero* exposures included clonazepam and acetaminophen at unspecified times. Vaginal delivery was induced at 38 weeks gestation because of toxemia. There were no congenital anomalies, but the neonate was initially jaundiced. (ISR# 4761022)

There were no cases reporting overdose as an adverse event. Adderall labeling, dated June 2005, states "only in rare cases will it be necessary to exceed a total of 40 mg per day." Thus, labeling does not state an absolute maximum daily dose. Dosages greater than 40 mg/day were reported in two cases, one with 45 mg/day, and one with 60 mg/day. The *in utero* exposure described above is the case reporting that the mother took 45 mg/day Adderall. The dosage of 60 mg/day was reported in a case of generic lack of effect in a 13-year-old male (ISR# 4492407).

Concomitant drugs used at the time of the adverse event in the 20 cases reporting adverse events other than lack of effect were paroxetine (2), atomoxetine, methylphenidate, oxcarbazepine, clonazepam (2), divalproex sodium, acetaminophen, stool softener, vitamins, and none. There is no pattern of concomitant drug use to suggest a specific interaction.

SUMMARY/CONCLUSIONS

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 found 98 reports. Of these 98 reports, there were 27 unique cases reported in patients aged 0 to 16 who were taking immediate-release mixed amphetamine salts or an unknown formulation. A second AERS search that included both Adderall and Adderall XR found three additional Adderall XR cases but no additional immediate-release mixed amphetamine salts cases. The additional cases were found because the drug list used to search AERS for this review contained more Adderall XR verbatim terms than the drug list used to search AERS for the Adderall XR review. The three additional Adderall XR cases are summarized in Attachment 2, but are not discussed in

this document. These three cases comprise one death that may have been cardiac in nature and two reports of panic and anxiety. The 27 immediate-release mixed amphetamine salts cases present an adverse event profile that is qualitatively similar to that of Adderall XR. As with Adderall XR[4] and methylphenidate,[5] the main categories of AEs reported are cardiovascular, psychiatric, and neurological. Neurological AEs are labeled; cardiovascular and psychiatric AEs are being explored further by DDRE, as described in the bullet points below. There were two deaths, both cardiac events in patients found on autopsy to have cardiac anomalies.

Mixed amphetamine salts product labels include seizure, dyskinesia, and exacerbation of tics and Tourette's syndrome. Methylphenidate labels list Tourette's syndrome as a rare AE without describing the effect as exacerbation. DDRE will recommend to DPP that updating relevant stimulant labels be considered to ensure consistency in describing these events.

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- 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. The Adderall XR review, this immediate-release mixed amphetamine salts review, and the results of the extensive review of psychiatric adverse events that was undertaken by ODS since September 2005 will be presented to the Pediatric Advisory Committee.

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[4] Phelan. Adderall XR one-year post-pediatric exclusivity postmarketing adverse event review. January 5, 2006. PID# D040761

[5] Phelan. Concerta one-year post-pediatric exclusivity postmarketing adverse event review and Adverse events with methylphenidate products other than Concerta in pediatric patients during the first year after granting of pediatric exclusivity for Concerta. June 14, 2005. PID# D040058 and PID# D050249.

signed January 27, 2006
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Safety Evaluator

Concur:
signed January 27, 2006
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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 or in which formulation is unclear (N=27)
2. Three cases of adverse events with Adderall XR that were found in the search for this document and were not included in the Adderall XR 1-year post-pediatric exclusivity postmarketing adverse event review

Attachment 1: Adverse event cases associated with immediate-release mixed amphetamine salts or in which formulation is unknown (N=27)

Cardiovascular Adverse Events (N=6)			
ISR#	**Age (yrs)**	**Gender**	**Summary**
4790953	10	Male	Supraventricular tachycardia requiring hospitalization with heart rate 250 bpm, dizziness, and chest pain after about 1 year Adderall 20 mg/day to treat ADHD. History of palpitation during use of Adderall and during use of methylphenidate. Adderall was discontinued, event is ongoing.
4648776	12	Female	Sudden cardiac death while running after 5 months Adderall 30 mg/day for an unknown indication. Concomitant atomoxetine. Autopsy found a "genetic cardiac problem."
4619565	16	Female	"Heart beating weird" and tingling sensation during use of Adderall. Adderall was discontinued and the events resolved. Concomitant clonazepam and divalproex sodium. Adderall dosage, duration, and indication unknown.
4597574	7	Male	Death attributed to cardiac arrhythmia after 3 weeks Adderall at an unknown dosage to treat ADHD. Autopsy found bicuspid aortic valve. Patient had history of infantile heart murmur.
4514240	15	Male	Fibrillation with heart rate over 200 bpm measured by mother on 5 occasions after about 2 years Adderall 20 mg/day to treat ADHD. Wore an unspecified monitor for 1 month which showed no further events. Adderall was discontinued.
4610960	7	Male	Heart pain on 3 occasions during 3 months Adderall 10 to 20 mg/day to treat ADD. Right bundle branch block per EKG. Adderall discontinued, no further heart pains.
Psychiatric Adverse Events (N=4)			
ISR#	**Age (yrs)**	**Gender**	**Summary**
4775675	9	Male	Uncontrollable tantrums, hitting, lashing out, anorexia after 6 months Adderall at an unknown dosage to treat ADHD and 2 months oxcarbazepine to treat bipolar disorder. Adderall was discontinued and events resolved.
4761022	5	Male	Oppositional defiant disorder in child who had been exposed to Adderall *in utero* during the first 5 months of pregnancy. The mother was taking 45 mg/day Adderall to treat ADHD.

ISR#	Age (yrs)	Gender	Summary
4601058	14	Male	Mania and suicidal ideation after less than 2 weeks generic mixed amphetamine salts 15 mg/day to treat ADD. Events did not occur during use of trade Adderall and resolved after discontinuation of generic product. A cousin had a similar experience.
4597573	15	Male	Violence and manic symptoms during use of various stimulants, including Adderall at an unspecified time, and antidepressants to treat anxiety, depression, and ADD. Stimulants and antidepressants were replaced with risperidone and events resolved. Father has bipolar disorder and patient was diagnosed with mood disorder nos and predisposition to bipolar disorder. Adderall dosage and duration unknown.
Neurological Adverse Events (N=6)			
ISR#	**Age (yrs)**	**Gender**	**Summary**
4711939	7	Male	Tic, migraine, insomnia, increased blood pressure, tachycardia, weight loss within month of starting Adderall at an unknown dosage to treat ADHD. Duodenal ulcer after 1 year Adderall. Tic subsided and exacerbated with dosage. Ritalin replaced Adderall. Outcome of events is unknown.
4696797	10	Female	Tic and lack of effect during 1 month generic mixed amphetamine salts 25 mg/day to treat ADD. Tic subsided with brand Adderall.
4589270	8	Male	Severe tic and movement disorder after less than 1 year Adderall 5 mg/day to treat ADHD. Events resolved over 6 months after Adderall was discontinued. Events recurred the same day Adderall was restarted.
4711476	14	Male	Absence seizures after several months Adderall. Dosage, indication, and outcome unknown.
4589349	8-10	Male	Tics, Tourette's disorder, movement disorder, occasional loss of consciousness, hyperventilation during use of Adderall 15 to 30 mg/day to treat ADD. Events abated when Adderall was discontinued and recurred when Adderall was restarted.
4589152	9	Male	Seizures during sleep and twitching during day after about 1 year Adderall. Dosage, indication, outcome unknown.

Dermatological Adverse Events (N=2)			
ISR#	**Age (yrs)**	**Gender**	**Summary**
4518987	12	Male	Rashes all over body, difficulty breathing, and "cardiac issues" requiring emergency care an unspecified time after starting Adderall 25 mg/day to treat ADD. Adderall discontinued, event resolved.
4827800	7	Male	Stevens Johnson Syndrome after 3 weeks Adderall. Concomitant methylphenidate. Adderall dosage and indication unknown.
Other Adverse Events (N=2)			
ISR#	**Age (yrs)**	**Gender**	**Summary**
4574550	13	Male	Gingival hyperplasia during use of Adderall and paroxetine. Dosage and indication of Adderall and timing and outcome of event are unknown.
4827801	10	Male	Suspected glaucoma after years of Adderall 20 mg/day to treat ADHD. No concomitant medications. No other medical conditions. Family history of glaucoma. Adderall discontinued, event ongoing.
Generic lack of effect (N=7)			
ISR#	**Age (yrs)**	**Gender**	**Summary**
4588451	9	Female	Generic mixed amphetamine salts was not effective. Trade Adderall is effective but patient requires higher dosage than insurance is allowing. Current dosage is 20 mg/day to treat ADD.
4578793	7	Male	Generic mixed amphetamine salts 10 mg/day was not effective to treat ADHD. Trade Adderall provides more stable results.
4578319	7	Female	Generic mixed amphetamine salts is not effective to treat patient's ADHD. Trade Adderall was effective. Dosage unknown.
4583894	6	Male	Generic mixed amphetamine salts 15 mg/day is not effective to treat ADHD. Trade Adderall is effective and provides better emotional stability.
4679214	5	Male	Generic mixed amphetamine salts 30 mg/day was not effective to treat ADD. Trade Adderall is effective.

ISR#	Age (yrs)	Gender	Summary
4565113	13	Female	Generic mixed amphetamine salts 20 mg/day is not effective to treat ADHD.
4492407	12	Male	Generic mixed amphetamine salts 60 mg/day was not effective to treat ADHD. Trade Adderall is effective.

Attachment 2: Three cases of adverse events with Adderall XR that were found in the search for this document and were not included in the Adderall XR 1-year post-pediatric exclusivity postmarketing adverse event review[6]

The additional cases were found because the drug list used to search AERS for this review contained more Adderall XR verbatim terms than the drug list used to search AERS for the Adderall XR review.

ISR# 4571913, MFR# SUS1-2005-00015, U.S.
Death occurred in a 14-year-old male after approximately 3 years treatment of ADHD with Adderall XR. The patient made some unusual movements and collapsed at school. He developed ventricular fibrillation, was revived, and was hospitalized. He was maintained on full support even though he could breathe on his own. Treatment included blood pressure medicines, afterload reduction, and pressor therapy. After medications were discontinued, the patient had some premature ventricular contractions. He died after 10 days. He had no arrhythmias at the time of death and autopsy was refused. There was no history of palpitation, dizziness, syncope, nausea, cold sweats, shortness of breath, chest pain, obesity, cigarette, alcohol, or illicit substance use. There were no concomitant medications.

ISR# 4571903, MFR# SUS1-2004-00862, U.S.
A 6-year-old male experienced a panic attack, including hyperventilation, increased heart rate, and anxiety, after one dose of Adderall XR 25 mg to treat ADHD. The patient was in foster care and had pre-existing stress and anxiety. The panic attack resolved; Adderall XR was discontinued. Concomitant medications were atomoxetine and fluoride.

ISR# 4502721, MFR# SUS1-2004-00632, U.S.
A 7-year-old female was started on Adderall XR, 5 mg/day, in January 2004. In May 2004, the dosage was increased to 10 mg/day. In May, she began having episodes of urinary incontinence. In June, she began having 8-10 debilitating panic/fear episodes per day. The patient also began stealing, complained of racing heart, became disruptive in class, and did not eat. Adderall XR was discontinued and the patient experienced withdrawal symptoms that included constipation, delusions, anxiety, and racing heartbeat. Since discontinuation, the patient had tonic seizures, increased ADHD symptoms, and continuing panic/anxiety episodes. The pediatrician suspects post-traumatic stress disorder.

[6] Phelan. Adderall XR one-year post-pediatric exclusivity postmarketing adverse event review. January 5, 2006. PID# D040761

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