Clinical Psychiatry/Psychopharmacology Review
BPCA Summary Review

PRODUCT (Generic Name):	Mixed Salts of Amphetamine
PRODUCT (Brand Name):	Adderall XR
DOSAGE FORM:	Extended Release Tablets
DOSAGE STRENGTHS:	5, 10, 15, 20, 25, 30, and 40-mg capsules
NDA:	21-303 SE5-009
NDA TYPE:	Supplement for ADHD in adolescents in response to FDA Pediatric Written Request Letter
SUBMISSION DATE:	September 17, 2004
SPONSOR:	Shire Laboratories, Inc.
OND DIVISION:	Division of Neuropharmacological Drug Products

Executive Summary

1.0 BACKGROUND

Adderall XR is an extended-release formulation of Adderall®. Adderall XR is described as mixed salts of amphetamine and includes the neutral sulfate salts of dextroamphetamine and amphetamine, the dextro isomer of amphetamine saccharate, and the mixed d- and l-amphetamine aspartate monohydrate.

Adderall XR is approved for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in children aged 6-12 years and in adults. This submission provides data to support a claim that Adderall XR is safe and effective in the treatment of ADHD in adolescents aged 13-17 years. This submission also comes to the Division as a response to a Pediatric Written Request (PWR) that was issued May 6, 2003. The review of this submission was therefore required to be performed on a priority basis.

The submission contains clinical results from a pharmacokinetic (PK) study and a placebo controlled fixed-dose study of adolescents with ADHD with doses ranging from 10-60-mg/day.

This memo summarizes primary reviews from the clinical, statistical, biopharmaceutics and chemistry teams.

2.0 CHEMISTRY

The primary Chemistry Team reviewer was Chhagan Tele, PhD. He recommends that the supplement may be approved from a chemistry standpoint. There were no changes in the HOW SUPPLIED or DESCRIPTION sections of labeling.

3.0 PHARMACOLOGY

Adderall XR is an approved product. There were no preclinical pharmacology data reviewed for this submission.

4.0 BIOPHARMACEUTICS

The single PK study in this submission was SLI381-110. The study was reviewed by Kofi Kumi, PhD of OCPB. This study included 23 adolescents aged 13-17 years with ADHD. The study was an open-label single-dose study with 3-treatment periods randomized crossover. There was a 7-day washout period in between these treatments. It included two cohorts of subjects-greater than and less than 75-Kg.

Dr Kumi states in his review:
"The pharmacokinetics of d- and l- amphetamine after administration of Adderall XR are linear over single oral doses ranging from 10 mg to 40 mg in adolescent ADHD patients weighing < 75 kg/165 lbs. The pharmacokinetics of d- and l-amphetamine are linear over doses ranging from 20 to 60 mg in adolescent (13 - 17 years) ADHD patients weighing > 75 kg/165lbs. In adolescents, the range of dose normalized Cmax, dose-normalized AUC, Cl/F and Vz/F was similar in males and females for both d- and l-amphetamine. In the adolescents, exposure measured by AUC was not affected by age. However, there was a decrease in Cmax for both d- and l- amphetamine with age and a decrease in Cmax and AUC with increasing body weight.

Comparison of the pharmacokinetics of d- and l-amphetamine after oral administration of Adderall XR in pediatric (6-12 years) and adolescent (13 -17) ADHD patients and healthy adults (22 - 46 years) indicates that body weight was the primary determinant of apparent differences in the pharmacokinetics of d- and l-amphetamine across age range. Systemic exposure measured by AUC and Cmax decreased with increases in body weight. Contrasts between age groups showed that all of the significant differences in pharmacokinetics occurred between the pediatric population and the adolescent and/or adult populations. There were no significant differences between adolescents and adults."

Dr Kumi recommends an approval action from an OCPB standpoint.

5.0 CLINICAL DATA

June Cai, MD was the primary clinical reviewer on this supplement. The primary statistical reviewer was Kun He, PhD.

5.1 Efficacy Data

The sponsor presents data from the single study (SLI381-314) as the basis for the claim that Adderall XR is effective in the treatment of ADHD in adolescents. This study had two phases designated A and B. The trial had one 4-week double-blind treatment phase (part A), and followed by a 6-month open-label phase (part B). Part A was the source of efficacy data for the proposed claim and part B provided a source for safety data on growth.

Part A was the randomized, double-blind, parallel group, placebo-controlled trial conducted in 50 centers in the USA, evaluating the use of Adderall XR (fixed dose groups of 10, 20, 30, and 40 mg/day and placebo) in subjects (age 13-17) with Attention Deficit Hyperactivity Disorder (ADHD). The primary cohort (designed for the primary objective) consisted of subjects whose weights were less than or equal to 75 kg/165 lbs, and the secondary cohort (designed for the secondary objective and exploratory analysis) consisted of subjects whose weights were greater than 75 kg/165 lbs. In this latter cohort patients were treated with fixed doses of either Adderall XR 50 or 60-mg/day or placebo. A total of 329 subjects enrolled in the study, and resulted 327 randomized to the double-blind phase. The ITT population included 287 subjects in the primary cohort, and 40 subjects in the secondary cohort. The primary efficacy endpoint was the mean change in ADHD-RSIV total score from baseline at Week 4 (LOCF) in the ITT population. The primary analysis was an ANCOVA model with terms for treatment, site, and the corresponding baseline score as the covariate.

Completion rates in the study were very good with 93% of the placebo and 89% of the drug group completion in the primary cohort. The summary of the results follow in Table 1 (extracted from Dr He's review).

Table 1-Analyses of ADHD-RS-IV Total Score in the Primary Cohort (ITT-LOCF)

	Placebo (N=52)	**10 mg (N=54)**	**20 mg (N=53)**	**30 mg (N=58)**	**40 mg (N=61)**
Baseline					
Mean (SD)	35.1 (9.7)	34.9 (10.4)	33.9 (9.1)	35.1 (10.8)	32.6 (10.8)
Endpoint					
Mean (SD)	25.7 (13.4)	20.0 (11.8)	13.3 (10.3)	16.1 (11.0)	16.0 (11.2)
Mean change (SD)	**-9.4 (10.6)**	**-14.9 (12.1)**	**-20.7 (11.2)**	**-19.0 (11.1)**	**-16.5 (11.6)**
LS mean difference	--	**-5.59**	**-12.23**	**-9.23**	**-8.49**
(95% CI)	--	(-9.40, -1.77)	(-16.06, -8.39)	(-13.00, -5.46)	(-12.22, -4.76)
p-value	--	0.0043	<0.0001	<0.0001	<0.0001

There is a marked dose response between 10 and 20-mg/day, but the best effect of all measured doses (10-40-mg/day) appears to be at the 20-mg dose. The sponsor acknowledges this in their draft labeling.

The 50 and 60-mg/day dose groups for children who weighed greater than 75-Kg did not separate from placebo statistically and the mean change in the 60-mg group was roughly equal to placebo (see Table 2 below). The 50-mg group had roughly the same magnitude of a treatment difference as the 10-mg group in the light weight cohort (<75-Kg). Doses of less than 50-mg/day were not assessed in this cohort.

Table 2 Analyses of ADHD-RS-IV Total Score in the Secondary Cohort (ITT-LOCF)

	Placebo (N=15)	**50 mg (N=15)**	**60 mg (N=10)**
Baseline Mean (SD)	35.7 (8.7)	30.4 (10.2)	32.3 (8.6)
Endpoint Mean (SD) **Mean change (SD)** **LS mean difference (95% CI)** **p-value**	23.1 (13.1) **-12.5 (10.1)**	13.5 (8.9) **-16.9 (12.4)** **-5.63** (-17.08, 5.83) 0.3145	18.3 (11.5) **-14.0 (12.5)** **-1.41** (-13.97, 11.15) 0.8156

These data support the claim that Adderall XR is effective in the treatment of ADHD in adolescents and that there appeared to be no increased benefit at doses of greater than 20-mg/day. 20-mg/day appeared to be superior to 10-mg/day with roughly twice the improvement in efficacy measures.

5.2 Safety

There were no unlabeled or unexpected adverse events that were likely to be drug related that were detected in this submission.

There were no deaths during any part of either study.

Serious Adverse Events

There were three serious adverse events in the adolescent population in which Dr. Cai did not think drug-relatedness could be ruled out. One patient was reported in the initial submission while the other two were reported in the 4-month safety update. All were in open-label treatment so there is no reliable placebo comparison rate.

Patient 34-006, a 14-year-old female, developed depression after 6-months of treatment and was hospitalized for suicidal ideation (COSTART term-thinking abnormally) for a period of 5-days and discharged from the hospital. During her hospitalization, she was treated with sertraline and the Adderall XR 30-mg was discontinued. Dr Cai disagrees with the investigator's opinion that the event is "totally unrelated to the study drug". This case represents a positive de-challenge; however, Adderall XR treatment initiation was not temporally related to the initiation of the depressive episode and no re-challenge with Adderall was performed. I therefore believe that no causal connection can be made in this case.

Subject # 27-002, a 14 year-old female who continued on to Part B from Part A of SLI-381-314, developed major depressive disorder (COSTART term: depression) during the second month of treatment while on 40mg of Adderall XR. The subject discontinued from the study due to this event, but the sponsor reports it was resolved without sequelae. There was no re-challenge with Adderall.

Subject # 56-003, a 13 year-old female who continued on in a new study after Part B of SLI-381-314, developed suicidal ideation (COSTART term: depression) and was hospitalized two months after entering the new study (in addition to the 6-months treatment in part B) while on 30mg of Adderall XR. The patient discontinued from the study due to this event, and the sponsor reports it was resolved without sequelae, but there was no re-challenge with Adderall.

I do not see a suggestion of causality in these cases since two of them lack temporal association with the initiation of treatment. Two of the three cases are 6 to 8 months removed from the initiation of Adderall XR therapy and there was no re-challenge attempt. On the other hand, one can not absolutely prove lack of causality given the data. All things considered, I do not believe that these cases represent an as yet unseen signal for what could reasonably be considered as Adderall XR induced suicide related adverse events.

Vital Signs and ECG

Mean changes and tabulations of outliers for vital signs were compiled for both the PK and efficacy studies. Mean change and outlier analyses in the efficacy study did not produce clinically concerning increases in blood pressure, pulse, or ECG parameters. The PK study however did demonstrate peak increases in pulse and blood pressure at the 2-4 hour post dose measurements. Increases in pulse were approximately 10-bpm across most dose groups without any signal for dose dependence. On the other hand there appeared to be a suggestion of peak effect with dose dependence at the 2-hour post dose recording of systolic and diastolic blood pressure. The effect on systolic blood pressure seems to endure in the secondary cohort at 60-hours post dose. These are included in the table below. I do not believe that these represent new findings.

Subjects & Cohorts		Adderall XR Groups					
		Primary Cohort			Secondary Cohort		
Dose Groups		**10mg**	**20mg**	**40mg**	**20mg**	**40mg**	**60mg**
Total N in Each Group		15	15	15	6	6	6
Systolic Blood Pressure Changes(mmHg)	**Baseline**	107.1	109.6	108.9	111.5	109.3	107.7
	@ 2-hour	4.7	12.4	17.7	8.0	25.7	18.7
	@ 4-hour	6.3	7.7	20.9	12.7	25.0	20.3
	@ 24-hour	3.1	2.3	7.1	6.0	7.8	13.2
	@ 60-hour	7.7	8.5	8.9	8.0	11.8	17.5
Diastolic	**Baseline**	60.6	60.4	63.8	58.7	59.2	60.7
Blood Pressure Changes (mmHg)	**@ 2-hour**	0.1	7.0	8.5	5.7	11.3	10.0
	@ 4-hour	2.6	8.5	7.7	2.8	8.8	9.7
	@ 24-hour	3.1	3.1	2.9	0.3	5.5	4.3
	@ 60-hour	3.5	6.8	3.5	4.7	5.5	8.8

Laboratory Analytes

There were a few statistically significant differences between Adderall XR and placebo with respect to laboratory analytes; however, Dr. Cai felt that none were clinically significant and I concur. Dr Cai noted the lack of serum creatinine data in this submission. Dr Cai states that the sponsor should explore this analyte during future studies but does not suggest that this deficiency would impede approval of this supplement. I agree that the lack of creatinine data in this submission should not impede its approval. In a MEDLINE search using amphetamine or Adderall and creatinine, there were no reports of renal impairment associated with therapeutic amphetamine use. It is, however, reasonable to ask the sponsor why they did not include serum creatinine as part of the clinical laboratory profile for these studies. Dr Cai notes that in another ongoing Adderall study in adult patients serum creatinine values are included.

Growth

Weight loss with the initial use of amphetamine is a common treatment emergent event. There was significant weight loss between all dose groups and placebo in the 4-week controlled trial. These changes were dose related with a maximum mean difference between the 60-mg/day and placebo groups in weight loss of 10.0 pounds over the 4-week period. Characterizing the long-term effects of amphetamine on growth and development is a much more important question. In the 6-month data there was a statistically significant difference in z-score for weight and BMI over the observation period. There was a significant decrease in the z-score for patients in the upper 75th percentile of height, but not for those in the 25-75th or below the 25th percentile group.

The lack of change in height is not particularly reassuring as it was measured over a period as short as 6-months; however, the sponsor is generating much more definitive 2-year data that will better examine the effects of amphetamine treatment on both height and Tanner staging.

6.0 WORLD LITERATURE

Dr Cai found that the sponsor provided a list of references from a world literature search but did not include the dates included for the search or a review and comment on their contents. The sponsor must provide a review and comment on the literature search prior to approval of this submission.

7.0 FOREIGN REGULATORY ACTIONS

On February 9, 2005 Health Canada suspended the marketing of Adderall XR. This action was based on the report of what Health Canada identified as sudden death and stroke in children and adults. The Health Canada alert stated:

> Health Canada's decision comes as a result of a thorough review of safety information provided by the manufacturer, which indicated there were 20 international reports of sudden death in patients taking either ADDERALL® (sold in the United States, not in Canada) or ADDERALL XR® (sold in Canada). These deaths were not associated with overdose, misuse or abuse. Fourteen deaths occurred in children, and six deaths in adults. There were 12 reports of stroke, two of which occurred in children. None of the reported deaths or strokes occurred in Canada.
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> A preliminary review of safety data for the other related stimulants authorized for use in the treatment of ADHD in Canada has been conducted. In that review, the incidence of serious adverse reactions leading to death was higher in ADDERALL® and ADDERALL XR combined than in the other drugs of this class.

Health Canada contacted the Division prior to taking their action. The Division was able to clarify what cases were reviewed by Health Canada and found that the cases in question were known to the Division, the Office of Drug Safety (ODS), and the Division of Drug Risk and Evaluation (DDRE) at the FDA. The FDA concluded that given the same data, the FDA did not agree with the conclusion reached by Health Canada that the risks associated with the use of Adderall XR outweighed its benefits. The Agency also decided that it would not remove Adderall XR from the market; however, given Health Canada's action, the FDA issued a Public Health Alert. The FDA Public Health Alert stated:

> Health Canada, the Canadian drug regulatory agency, has suspended the sale of Adderall XR in the Canadian market. Adderall XR is a controlled release amphetamine used to treat patients with Attention Deficit Hyperactivity Disorder (ADHD). The Canadian action was based on U.S. post-marketing reports of sudden deaths in pediatric patients.
>
> Adderall XR is approved in the United States for the treatment of adults and pediatric patients 6 years of age and older with ADHD, and Adderall, the immediate-release formulation of the drug, is approved for pediatric patients with ADHD. The Food and Drug Administration (FDA) has been aware of these post-marketing cases, and evaluated the risk of sudden death with Adderall XR prior to approving the drug for treatment of ADHD in adults last year.

Of 12 total cases, five occurred in patients with underlying structural heart defects (abnormal arteries or valves, abnormally thickened walls, etc.), all conditions that increase the risk for sudden death. Several of the remaining cases presented problems of interpretation, including a family history of ventricular tachycardia, association of death with heat exhaustion, dehydration and near-drowning, very rigorous exercise, fatty liver, heart attack, and type 1 diabetes mellitus. One case was reported three to four years after the event and another had above-toxic blood levels of amphetamine. The duration of treatment varied from one day to 8 years. The number of cases of sudden deaths reported for Adderall is only slightly greater, per million prescriptions, than the number reported for methylphenidate products, which are also commonly used to treat pediatric patients with ADHD.

The FDA is continuing to evaluate these and other post-marketing reports of serious adverse events in children, adolescents, and adults being treated with Adderall and related products. When one considers the rate of sudden death in pediatric patients treated with Adderall products based on the approximately (b)(4) prescriptions written between 1999 and 2003 (the period of time ese deaths occurred), it does not appear that the number of deaths reported is greater than the number of sudden deaths that would be expected to occur in this population without treatment. For this reason, the FDA has not decided to take any further regulatory action at this time. However, because it appeared that patients with underlying heart defects might be at increased risk for sudden death, the labeling for Adderall XR was changed in August 2004 to include a warning that these patients might be at particular risk, and that these patients should ordinarily not be treated with Adderall products.

The alerts from Health Canada (HC) and the FDA differ in the reported number of cases of sudden unexplained death (SUD). HC reports 20 cases where the FDA reports 12. The 20 deaths from the HC report include 14 children and 6 adults. The FDA Public Health Advisory focuses on the 12 deaths in children for two primary reasons. First, the FDA had already performed an extensive review of post marketing adverse events in adults prior to the approval of Adderall XR in the adult population with ADHD. The reporting rate for SUD in adults was well below the reported background rate for SUD in the adult population; therefore, the adult deaths were not mentioned in the advisory. Secondly, the background rates for SUD in children were less reliable, so less could be said about the comparative rates of reports of SUD for pediatric patients on drug versus the naturally occurring event without amphetamine treatment.

The FDA case count for SUD in pediatric patients whose demise was uncomplicated by abuse, overdose, or misuse differed by two with HC (HC-n=14, FDA-n=12). By the FDA's accounting one of the 14 Canadian cases was counted twice (STX1-2002-00145 and STX1-2001-00167 appear to be the same patient). The other case counted

by HC but not by FDA was (SUS1-2003-00501). Though HC also excluded cases of overdose misuse or abuse this patient had been abusing cocaine for the two-weeks prior to his death and was therefore not counted by the FDA.

As noted above, a warning statement about the risk of death in patients with underlying structural heart disease was incorporated into the US labeling for Adderall XR with the approval for its use in the adult ADHD population. This FDA action was taken prior to Health Canada's suspension of Adderall XR marketing. Therefore given the Agency's recent in-depth investigation of post-marketing reports of death and serious cardiovascular related adverse events during the review of the adult ADHD application, the extensive discussions with Drs, Katz, Temple, Galson, Jenkins and Office of Drug Safety, the Division of Drug Risk and Evaluation and Health Canada officials, and the recent publication of new labeling, the Public Health Advisory, Patient Information, and Prescriber Information for Adderall XR, I do not recommend any further action at this time.

8.0 CONCLUSIONS AND RECOMMENDATIONS

I believe that the sponsor has presented data that support the claim that Adderall XR is effective in the treatment of ADHD in the adolescent population (aged 13-17 years). This study showed a peak therapeutic effect at a dose of 20-mg/day. Clinical benefit at 20-mg/day as measured by the ADHD-RS was roughly twice as good as at 10-mg; however, doses higher than 20-mg/day showed numerically less symptom relief than 20-mg/day. In order for this supplement to be approved the sponsor must address the following clinical comments and questions (b) (5)
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/s/

Paul Andreason

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