CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-303

MEDICAL REVIEW

REVIEW AND EVALUATION OF CLINICAL DATA

APPLICATION INFORMATION
NDA: 21-303
Sponsor: Shire Laboratories Inc.
Drug: Adderall XR (amphetamine product)
Material submitted: Original NDA
Date submitted: October 3, 2000
User fee due date: August 3, 2001
Medical officer: Andrew D. Mosholder, M.D.
Completion Date:

Contents

1.0 Material Reviewed

October 3, 2000, original NDA (data cutoff date August 15, 2000)
December 27, 2000, submission of investigator information
February 13, 2001, 4 month safety update (data cutoff date December 15, 2000)

2.0 Background

Related INDs and NDAs:

NDA 11-522(Shire) for Adderall

Administrative history: Adderall is a single entity amphetamine drug product, and its current labeling is based on that approved for all amphetamine products by the DESI committee in the early 1970's. The sponsor submitted the original IND application for this modified release formulation on 3/25/99. Representatives of Shire and of FDA met 7/20/99 to discuss the clinical development program for this product. A

pre-NDA meeting took place 8/16/00, and this application was submitted approximately seven weeks later.
Adderall XR has been referred to as SLI 381 during its development, and I will continue to use this designation for this review.

Proposed directions for use: This product is intended for once-a-day morning administration. For patients already receiving marketed Adderall, Shire's proposed labeling suggests [redacted] For patients 6 years old or older who are not receiving current Adderall treatment, the suggested starting dose is 10 mg, with titration at weekly intervals. The proposed labeling also indicates that the contents of the capsule may be sprinkled on food. In addition, the proposed labeling [redacted]

Financial disclosure: Tami Martin, R.N., has signed the Form 3454 on behalf of Shire certifying that no financial incentives were offered to any of the clinical investigators in exchange for specific results. Also, no investigator indicated any financial interests in Adderall XR.

3.0 Chemistry: The drug product is available in 10, 20 and 30 mg strengths. The capsules contain equal portions of immediate release pellets and delayed release pellets, to deliver two boluses of drug substance after ingestion. The immediate release pellets dissolve at low pH (corresponding to gastric pH) and the delayed release pellets dissolve at higher pH (corresponding to the pH of the small intestine). The pellets consist of the drug substance, hydroxypropyl methylcellulose, a [redacted] enteric coating polymer, and a sugar core. The capsules may be opened and the contents added to food.

The salts and isomers of the drug substance are in the same proportion as marketed Adderall, i.e., equal amounts of the following 4 components:
Dextroamphetamine Saccharate
Amphetamine Aspartate
Dextroamphetamine Sulfate
Amphetamine Sulfate.
Because amphetamine is a racemic mixture, this results in a 3:1 ratio of dextro-amphetamine to levo-amphetamine.

At the time of this writing, there are unresolved Good Manufacturing Process issues for the production of the drug product. Please refer to the Chemistry review for details.

4.0 Preclinical: As a relatively older drug, amphetamine has not undergone the extensive preclinical evaluation that is now routine for human drugs. The sponsor has submitted reports on their genetic and reproductive toxicity studies. In addition, Shire provided a literature survey of preclinical data with amphetamine. Among the

publications reviewed were a number of studies showing behavioral tetatogenicity of amphetamine, and these findings may be appropriate for labeling. Please refer to the Pharmacology review for details.

5.0 Clinical Data Sources

The following is a listing of the studies submitted.

Study	Description
Clinical Pharmacology studies	
371.404	Single dose crossover pharmacokinetic study of two test formulations and Adderall, n= 9 adult volunteers
102	Single dose crossover pharmacokinetic study of three test formulations and Adderall, n=20 adult volunteers
103	Single dose crossover pharmacokinetic study, SLI 381 30 mg fed, fasted, and sprinkled, n=21 adult volunteers
104	Single dose 2 way crossover pharmacokinetic study, 1-30 mg SLI 381 versus 3-10 mg SLI 381, n=20 children with ADHD
105	Multiple dose pharmacokinetic study, 30 mg SLI 381 X 7 days, n=20 adult volunteers
Clinical Trials	
201	Multicenter, randomized, double blind, placebo controlled 5-way crossover trial; 1 week of once-a-day Adderall 10 mg; SLI 381 10, 20, 30 mg; and placebo; n=51 children with ADHD
301	Multicenter, randomized, double blind, placebo controlled, parallel group, 4-arm trial; SLI 381 10 mg/day, 20 mg/day and 30 mg/day, and placebo; n=584 children with ADHD
302	Open label treatment with SLI 381 10, 20, or 30 mg/day for up to 2 years; n=566 (ongoing)

Number of subjects:The following table is adapted from the sponsor's Table 8.1.1 in the safety update.

Number of subjects according to type of study and treatment

Type of study	SLI 381	Marketed Adderall	Placebo
Single dose PK- adults	50	28	0
Single dose PK-children	20	0	0
Multiple dose PK-adults	20	0	0
Safety and efficacy trials-children	553	48	259
Total	643	76	259

It should be noted that 128 children received placebo in study 301 and subsequently received open label SLI 381 in study 302; thus, these subjects are listed twice here, under both placebo and SLI 381.

Demographics

In the pharmacokinetic studies, the 70 adult volunteers were between 18 and 55 years of age and were predominantly Caucasian males. The 20 children who participated in the pediatric pharmacokinetic study were also predominantly Caucasian males, and were between 6 and 12 years of age.

For the phase 2-3 studies, (i.e., studies 201, 301, and 302), the demographic characteristics are shown below.

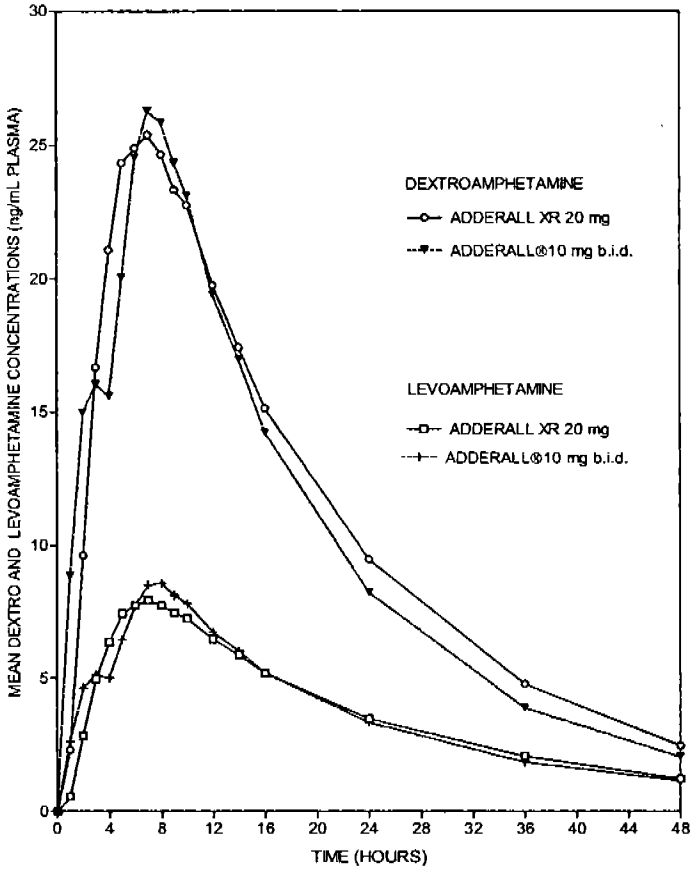
Characteristic	SLI 381 (n=553)	Adderall (n=48)	Placebo (n=259)
Age (yrs)			
Mean	8.6	9.5	8.7
Range	6-12	6-12	6-12
Sex (number male:female)	432:121	42:6	196:63
Ethnic origin (n)			
Caucasian	406	22	183
African-American	68	8	37
Hispanic	55	12	27
Other	24	6	12
ADHD type (n)	517	47	245
Combined	27	1	9
Hyperactive	9	0	5
Inattentive			
Patients with a psychiatric comorbidity (n)	161	10	75
No prior psychotropic drug use (n)	172	0	81

The subjects were predominantly males (as expected based on the epidemiology of ADHD) and were predominantly Caucasian. Approximately one-third were naïve to drug treatment of ADHD.

Extent of exposure: Of the 553 children exposed in clinical trials by the time of the safety update, 195 received SLI 381 for more than 6 months, and 336 for more than 3 months. A total of 196 children were exposed to the highest dose (30 mg/day), but 109 of these 196 subjects received 30 mg/day for only a week or less.

6.0 Pharmacokinetics

The figure below (from Shire's draft labeling) shows the plasma concentration-time curves for a single 20 mg dose of SLI 381 compared to marketed Adderall 10 mg, administered in two doses four hours apart. The data are from protocol 102, and the subjects were 20 adult volunteers.



The table below summarizes the pharmacokinetic results obtained in study 201.

Pharmacokinetic results obtained from study 201 following multiple dosing (n= 51 children with ADHD). Adapted from Shire's draft labeling.

Treatment	Dextroamphetamine			Levoamphetamine		
	AUC_{0-24} (ng·hr/mL)	T_{max} (hours)	C_{max} (ng/mL)	AUC_{0-24} (ng·hr/mL)	T_{max} (hours)	C_{max} (ng/mL)
SLI 381 (10 mg)	432	6.4	28.8	138	6.4	8.8
SLI 381 (20 mg)	777	5.8	54.6	262	5.7	17.2
SLI 381 (30 mg)	1364	5.5	89.0	444	5.5	28.1
ADDERALL® (10 mg)	423	3.3	33.8	143	3.2	10.6

In study 103, a high fat meal delayed the mean tmax following a 30 mg dose by 2.5 hours.

7.0 Efficacy

7.1 Study 201

7.1.1 Investigators/sites:

Site	Investigator	Location
1	J. Biederman, M.D.	Massachusetts General Hospital, Boston MA
2	L. L. Greenhill, M.D.	New York State Psychiatric Institute, New York NY
3	J. T. McCracken, M.D.	UCLA Neuropsychiatric Institute, Los Angeles CA
4	J. M. Swanson, Ph.D.	University of California-Irvine, Irvine CA

7.1.2 Objective: The purpose of this study was to assess the safety and efficacy of three doses of SLI 381, compared to placebo and marketed Adderall, with all study treatments administered once daily.

7.1.3 Population: The intended sample size was 60 subjects. To be eligible, subjects were to be 6 -12 years old, with a primary diagnosis of ADHD, combined or hyperactive-impulsive subtype. Subjects were to be receiving stimulant medication for ADHD prior to the study. Seizures, tic disorders, aggressive behavior, substance abuse, hyperthyroidism, glaucoma, significant medical illness, and comorbid psychiatric disorders were among the exclusion criteria.

7.1.4 Design: This was a randomized, double blind, 5 treatment crossover study. Each subject received each of the 5 treatments for one week, in random order. Assessments of treatment response were to be obtained in laboratory classroom settings. Following screening procedures all subjects were to participate in a practice session, involving a single dose of SLI 381 20 mg and laboratory classroom assessments. Subjects who tolerated this test dose were to be randomized to double blind treatment, with laboratory classroom assessments (including vital signs, pharmacokinetic sampling and efficacy ratings) occurring each Saturday. The one-week treatment conditions were placebo, marketed Adderall 10 mg, and SLI 381 10, 20 and 30 mg; each study medication was to be administered once daily in the morning. Concomitant psychotropic medications were prohibited. A sixth crossover period was included in the design to allow a makeup week for subjects who missed one of the previous weeks; subjects who did not need to makeup a treatment arm received a randomly selected second week of a previous treatment.

7.1.5 Analysis plan: The SKAMP was the primary efficacy measure. Repeated measures analysis of variance with session and medication as the independent variables was the specified analytic method.

7.1.6 Results

Demographics: Fifty one subjects were randomized, and 49 of these were assessed

post-randomization and were thereby included in the Intent-to-treat sample. The following is a summary of the demographic characteristics of the 51 randomized patients.

Age (yrs) Mean Range	 9.5 6-12
Ethnic origin (n) Caucasian Asian African-American Hispanic Other	 25 3 8 12 3
Male (n) Female (n)	44 7
ADHD subtype (n) Hyperactive Combined	 1 50

Note that the majority of subjects were male, with ADHD combined subtype.

Patient disposition

The table below summarizes the disposition of the 51 subjects.

Reason for discontinuation	Number of subjects
Completed study	44
Adverse event	2
Lack of efficacy	0
Withdrew consent	1
Lost to follow up	2
Other	2

Although the protocol allowed subjects to make up a treatment week that they had missed, this was provision was not used, and subjects instead received an extra week of a treatment they had previously received.

Concomitant medications: The sponsor provided a line listing of concomitant medications administered, but no summary was provided.

Efficacy measures: The following table shows the time points at which there was a statistically significant difference between the drug and placebo on mean SKAMP rating scores (not corrected for multiple comparisons). At time=0, the mean scores for placebo on both attention and deportment were numerically lower (better) than for any drug group, but if this caused any bias it would have been against finding a drug effect.

SKAMP-Attention

Timepoint	Adderall 10 mg	SLI 381 10 mg	SLI 381 20 mg	SLI 381 30 mg
1.5 hr	+			
4.5 hr	+	+	+	+
6 hr	+	+	+	+
7.5 hr	+	+	+	+
9 hr			+	+
10.5 hr		+	+	+
12 hr			+	+

SKAMP-Deportment

Timepoint	Adderall 10 mg	SLI 381 10 mg	SLI 381 20 mg	SLI 381 30 mg
1.5 hr	+		+	+
4.5 hr	+	+	+	+
6 hr	+	+	+	+
7.5 hr	+	+	+	+
9 hr	+	+	+	+
10.5 hr	+		+	+
12 hr				+

Note that the immediate release Adderall showed an effect at the earliest timepoint, and that it separated from placebo for 7.5 hours on the attention scale. The higher doses of SLI 381 appeared to show a longer duration of effect (up to 12 hours).

The pharmacokinetic results of this trial are summarized above in section 6.0.

7.1.7 Conclusions: This trial provides clear evidence of an effect of SLI 381 in the treatment of ADHD. It is somewhat problematic, however, to specify the time of onset and offset of the effect from these data, although the sponsor contends that this trial shows the duration of action to be 12 hours. For comparison, immediate release Adderall 10 mg was statistically separated from placebo for up to 7.5 hours, but in my opinion few clinicians would feel that a single 10 mg dose would be effective for that duration of time in a typical child with ADHD. This suggests that interpreting the data in this manner may not provide optimum external validity.

7.2 Study 301

7.2.1 Investigators/sites:

H. Abikoff, Ph.D., NYU Child Study Center, New York NY, site #50
P. Ahmann, M.D., Marshfield Clinic, Marshfield WI, site #59
P. J. Ambrosini, M.D., Eastern Pennsylvania Psychiatric Institute, Phila. PA, site #55
L.E. Arnold, M.D., and M. Aman, Ph.D., Ohio State University, Columbus OH, site #52
J. Biederman, M.D., Massachusetts General Hospital, Boston MA, site #05
M. Blum, D.O., Heart of America Research Institute, Mission KS, site #49
J. L. Blumer, M.D., Ph.D., University Hospitals of Cleveland, Cleveland OH
S. W. Boellner, M.D., Clinical Study Centers, Little Rock AK, site #07
L. Brown, M.D., and J. Elia, M.D., Children's Hospital of Philadelphia, Phila. PA, site #8
R. T. Brown, Ph.D., Medical University of South Carolina, Charleston SC, site#9
O. G. Bukstein, M.D., University of Pittsburgh Medical Center, Pittsburgh PA, site #52
C. D. Casat, M.D., Behavioral Health Center, Charlotte NC, site #10
M. C. Chandler, M.D., North Carolina Neuropsychiatry, Chapel Hill NC, site #12
E. Cherlin, M.D., Behavioral and Medical Research, El Centro CA, site #13
C. K. Conners, Ph.D., Duke University Medical Center, Durham NC, site #14
D. F. Connor, M.D., University of Massachusetts, Worcester MA, site #47
D. Coury, M.D., Pediatric Clinical Trials International, Columbus OH, site #15
A. J. Cutler, M.D., Coordinated Research of Florida, Winter Park FL, site #16
W. B. Daviss, M.D., and C. L. Donnelly, M.D., Dartmouth-Hitchcock Medical Center, Lebanon NH, site #17
C. Figueroa, M.D., Advanced Psychiatric Group, Rosemead CA, site #18
L. M. Frank, M.D., Monarch Research Associates, Virginia Beach VA, site #19
S. Grcevich, M.D., Family Medical Center by the Falls, Chargin Falls OH, site #66
L. Greenhill, M.D., NYSPI, New York NY, site #2 and #20
S. Helfing, M.D., Oregon Center for Clinical Investigations, Lake Oswego OR, site #21
S. L. Hirsch, M.D., Children's Memorial Hospital, Chicago IL, site #22
J. P. Horrigan, M.D., University of North Carolina, Chapel Hill NC, site #23
J Hudziak, M.D., Univ. of Vermont, Burlington VT, site #24
M Kremenitzer, M.D., Danbury CT, site #56
D. Lee, M.D., Emory University, Atlanta GA, site #57
M. Levin, M.D., San Ramon CA, site #63
K. S. Lewis, M.D., Barrow Neurological Group, Phoenix AZ, site #25
R. S. Lipetz, D.O., Encompass Clinical Research, Spring Valley CA, site #26
T. M. Lock, M.D., Children's Hospital of Buffalo, Buffalo NY, site #34
P. D. Londborg, M.D., Seattle Clinical Research Center, Seattle WA, site #27
F. A. Lopez, M.D., Children's Developmental Center, Maitland FL, site #28
K. McBurnett, Ph.D., University of Chicago, Chicago IL, site # 29
J T. McCracken, M.D., UCLA Neuropsychiatric Institute, Los Angeles CA, site #3 & #30
Denis Mee-Lee, M.D., Hawaii Clinical Research Center, Honolulu HI, site #61
J. Newcorn, M.D., Mt. Sinai Medical Center, New York NY, site #31
D. Palumbo, Ph.D., University of Rochester Medical Center, Rochester NY, site #32
A. Patel, M.D., Damluji Research Center, Vista CA, site #33
S. R. Pliszka,M.D., UTHSCSA, San Antonio TX, site #35
G. Realmuto, M.D., University of Minnesota Medical School, Minneapolis MN, site #53
M. Rosenthal, D.O., Behavioral and Medical Research, San Diego CA, site #48
R. L. Rubin, M.D., Miami Research Associates, Miami FL, site #38
K. Saylor, Ph.D., Neuro Science, Bethesda MD, site #51
L. Scahill, M.S.N., Ph.D., Yale Child Study Center, New Haven CT, site #39
T. M. Shiovitz, M.D., and P. D. Tigel, M.D., California Clinical Trials, Beverly Hills CA, site #40
W. T. Smith, M.D., Pacific Northwest Clinical Research, Portland OR, site #41
V. Spratlin, Mercer University, Atlanta GA, site #58
M. Sternberg, M.D., Woodbridge VA, site #54
J. J. Storlazzi, M.D., ADHD Behavioral Learning Disabilities Center, Wilmington DE, site #64
H. Tilker, Ph.D., and J.T. Cecil, M.D., Four Rivers Clinical Research, Paducah KY, site#43
S. Wigal, Ph.D., University of California-Irvine, Irvine CA, site #4 and #42

M. Wolraich, M.D., and S. Couch, M.D., Child Development Center, Nashville TN, site #45
D. R. Wynn, M.D., Consultants in Neurology, Northbrook IL, site #46

7.2.2 Objective: The purpose of this trial was to assess the safety and efficacy of SLI 381 versus placebo in the treatment of children with ADHD.

7.2.3 Population: The subjects were to be 450 children aged 6-12 years with ADHD, hyperactive-impulsive or combined subtype. The protocol required subjects to have the same schoolteacher in both morning and afternoon classes. Exclusion criteria included the following: significant psychiatric comorbidity, history of poor response to stimulants, seizures, tic disorder, substance abuse, hyperthyroidism, glaucoma, and allergy to Adderall.

7.2.4 Design: This was a multicenter, randomized, parallel group, 4-arm, placebo controlled trial. Prior to randomization subjects, were to receive a one-week single blind placebo washout. Following this, subjects were to be randomized to one of the following four treatments: SLI 381 10 mg/day, 20 mg/day, 30 mg/day, or placebo. The ratio for randomization was 2:2:2:3, to yield 100 subjects in each of the active treatment arms and 150 in the placebo arm. The duration of treatment was to be 3 weeks. If appropriate, subjects could be offered open label treatment with SLI 381 following this trial. The screening assessments included history and physical exam, clinical laboratories, ECG, psychiatric evaluation including the DISC, and pregnancy testing if indicated. Safety monitoring included vital signs at each visit, and end of treatment clinical laboratories and ECG. Concomitant medications were generally not allowed, except for bronchodilators.

The designated primary efficacy measure was the 10 item Conners Global Index Scale by the teacher (CGIS-T). Teachers were to phone in ratings of the subject in the morning and afternoon on Monday, Wednesday, and Friday of each week. With respect to the time period for reporting. the instructions to the teacher on the case report form were, "Rate each item according to how much of a problem it has been during this session." In other words, the case report form did not indicate a specific time period (e.g., Wednesday afternoon). As a secondary measure, parents were to complete the parental version of the Conners scale three times per day (at 10:00 am, 1:00 pm and 4:00 pm) on a Saturday or Sunday of each week. Additionally, parents completed a Global Assessment and the investigator completed a CGI rating.

7.2.5 Analysis: The intent to treat population was defined as subjects who had at least one post-randomization CGIS-T score. The primary efficacy measure was the average of the last week's CGIS-T scores (up to 6 individual scores, morning and afternoon on Monday, Wednesday and Friday). Morning and afternoon scores were also to be averaged separately. Analysis of covariance was to be employed, with treatment and site as independent variables and baseline score as a covariate.

7.2.6 Results

Patient disposition: A larger number of subjects were randomized than was specified in the protocol (564 randomized, versus 450 planned). The following table summarizes the reasons that patients discontinued prematurely from the study, by randomized treatment group.

Reason	30 mg (n=124)	20 mg (n=121)	10 mg (n=129)	Placebo (n=210)
Adverse event	5	4	0	6
Lack of efficacy	0	1	2	10
Consent withdrawn	4	7	4	11
Protocol violation	2	1	2	1
Lost to follow-up	0	2	0	6
Other	1	1	2	3
Total dropouts	12	16	10	37

The intent-to-treat population included 120 30 mg/day patients, 112 20 mg/day patients, 128 10 mg/day patients, and 203 placebo patients. The sponsor did not provide information on patient disposition by week.

Demographics and baseline characteristics:
The following table summarizes the baseline characteristics for the intent-to-treat sample.

Characteristic	30 mg (n=120)	20 mg (n=112)	10 mg (n=128)	Placebo (n=203)
Male:female (n)	96:24	90:22	100:28	148:55
Race (n)				
Caucasian	84	92	98	156
African American	20	9	11	27
Hispanic	11	10	12	14
Asian/PI	1	0	1	2
Native American	0	0	1	0
Other	4	1	5	4
Mean Age (yr)	8.8	8.4	8.5	8.6
Diagnostic type (n)				
Combined type	112	104	117	190
Hyperactive	6	6	8	8
Inattentive	2	2	3	5
No prior treatment (n)	37	34	48	76
No comorbidity (n)	83	81	87	142

Concomitant medications: The most commonly used concomitant medication during the trial was Tylenol, used by at least 10% of subjects in each group.

Efficacy results:
The mean change from baseline to endpoint on the CGIS-T (the primary outcome measure) by treatment group was as follows:

Treatment	Overall	Morning	Afternoon
Placebo	-0.9	-0.7	-1.2
10 mg	-5.3	-5.0	-5.4
20 mg	-6.0	-5.4	-6.8
30 mg	-6.4	-5.8	-7.2

All comparisons to placebo were highly statistically significant (p-value $\leq$0.0001). Furthermore, superiority over placebo for all three doses was statistically significant at weeks 1, 2, and 3 as well as at endpoint, for the weekly average CCGIS-T.

The results on the parent's CGIS were also highly statistically significant for superiority of all active treatments over placebo, at morning, afternoon and evening timepoints.

Boys on average had higher baseline CGIS-T scores and slightly greater mean improvement with active treatments than did girls. All doses were shown to be effective on the CGIS-T for both the subgroup of patients naïve to treatment and the subgroup of those previously treated.

Analysis of the subgroup of the first 450 subjects (i.e., the protocol specified number to be randomized) also showed superiority of all three doses over placebo, on the CGIST.

An agency inspection of Dr. Frank Lopez's site revealed some problems with documentation of the primary efficacy data; please refer to the letter from Dr. El-Hage of the Division of Scientific Investigations to Dr. Lopez (July 3, 2001). Generally speaking, the lapses in documentation reflected the fact that the subjects' teachers, and not staff involved in the trial, generated the efficacy ratings in this study.

7.2.7 Conclusions: This study provides evidence for the efficacy of all three doses studied in the treatment of ADHD.

8.0 Safety

8.1 Safety methods: This safety review is based primarily on the sponsor's Integrated Summary of Safety and Four Month Safety Update. At the time of the safety update, one clinical trial (study 302) was still ongoing; the cutoff date for including safety data from study 302 was 12/15/00. For ascertainment of common adverse events and drug related changes in monitored safety parameters, study 301, the parallel group study, is more informative by virtue of its design than is the crossover trial 201. Accordingly I will concentrate on the safety findings from study 301 in the following sections. In evaluating the findings described below with respect to vital signs, laboratories, and ECGs in study 301, it is important to recall that the baseline values for these parameters were obtained after a one-week placebo washout.

8.2 Deaths: There were no deaths in these studies.

8.3 Assessment of dropouts

8.3.1 Overall pattern of dropouts

The following table shows the pattern of premature discontinuations for the controlled efficacy trials, 201 and 301.

Reason for discontinuation	Percentage of patients discontinuing	
	SLI 318 (n=425)	Placebo (n=259)
Adverse events	2.4	2.7
Withdrawn consent	3.5	4.6
Protocol violation	1.2	0.4
Lost to follow up	0.7	2.3
Lack of efficacy	0.7	3.9
Other	1.4	1.2
Total	9.9	15.1

In the long term open label study (302), there was a higher proportion of dropouts (26.7%), with 10.1% of dropouts related to adverse events.

8.3.2 Adverse Events Associated with Dropout

The most frequent adverse events associated with dropout are shown below, with the incidence of dropout among the 553 pediatric patients treated with SLI 381 (source: safety update).

Adverse event	% of patients dropping out (n=553)
Anorexia	3.3
Insomnia	1.8
Weight loss	1.3
Emotional lability	1.1
Depression	0.7

Among the remaining adverse events associated with dropout, a few deserve particular mention. Subject 28-46 in study 302, an 11 year old boy, discontinued after loosing 20 lbs. Subject 11-10 in study 302, a 6 year old boy, developed new onset seizures. Two subjects in study 302 (28-24 and 16-03) discontinued because of tics.

8.4 Serious adverse events: There were four serious adverse events among patients who received SLI 381:

Subject 301/10-08--10 year old girl hospitalized for abdominal pain (final diagnosis constipation)
Subject 301/52-15--9 year old boy hospitalized for dehydration and gastroenteritis

Subject 302/11-18--10 year old boy hospitalized for antibiotic treatment of lymphadenitis
Subject 302/29-10--11 year old boy diagnosed with acute myelogenous leukemia

8.5 Other safety findings

8.5.1 Adverse event incidence

As the interpretation of adverse events in a crossover study is not straightforward, I will concentrate here on the findings from the parallel group study. The following is the sponsor's table of adverse events in study 301, pooling all doses of SLI 381 versus placebo. Adverse events shown had an incidence with drug of at least 1% and were also more frequent with drug than placebo.

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%

From this table, the following adverse events would meet the usual criteria for being common and drug related (i.e., relative risk of at least 2 and incidence with drug of at least 5%): fever, loss of appetite, emotional lability, insomnia, nervousness.

Dose related adverse events: In trial 301, the following adverse events were reported at an incidence of at least 5% in the high dose group, and also appeared to show a dose related pattern of incidence:

Adverse event	Incidence (%)			
	Placebo	10 mg	20 mg	30 mg
Anorexia	11.4	16.3	23.1	26.6
Weight loss	0	1.6	2.5	8.9
Insomnia	1.9	11.6	19.0	19.4

8.5.2 Laboratory findings: No patients discontinued because of laboratory

abnormalities. In the placebo controlled parallel group study 301, the following treatment emergent laboratory value abnormalities occurred at the end of treatment in at least 1% of SLI 381 treated patients, with a relative risk of at least 2 compared to placebo:

Laboratory abnormalitiy	SLI 381 incidence (%)	Placebo incidence (%)
High albumin	2.9	1.0
Low BUN	1.6	0.5
High protein	3.7	1.0

In addition, 36 drug treated subjects and 6 placebo treated subjects had end of study calcium values that were abnormally high; however, a large number of subjects had abnormally high calcium values at baseline, and it was not clear from the study report or the Integrated Summary of Safety if the abnormal values were treatment-emergent or not.

Shire also provided an analysis of mean change from baseline in laboratory values. The following changes from baseline among drug treated groups were statistically significant compared to placebo:
Increased: albumin, creatinine, bilirubin, total protein, RBC count, hematocrit, and hemoglobin.
Decreased: SGOT, SGPT
Shire concluded that all of these mean changes were of modest degree and not likely to be clinically relevant.

Shire also presented data on long term changes in laboratory parameters in the open label study 302; however, the baseline values for these analyses were the values obtained at the end of study 301, so they were not unexposed values (except for the placebo patients). Most of the mean changes observed were of a small magnitude; however, the mean alkaline phosphatase decreased over 6 months from a baseline of 256 IU/L to 226 IU/L.

8.5.3 Vital signs, height and weight

In the parallel group study (301), there were no statistically significant changes in pulse or blood pressure from baseline, for any dose of active drug versus placebo. The sponsor did not provide an analysis of height or weight data from study 301.

In the laboratory classroom study (201), sitting blood pressure and pulse were measured at 0, 1.5, 4.5 and 7.5 hours. The mean pulse rate increased by 14-18 bpm for all treatment groups including placebo. For blood pressure, the greatest difference between drug and placebo was for the 30 mg SLI 318 group in sitting systolic blood pressure at 1.5 hours (change of +7 mmHg for drug versus –1 mmHg for placebo).

In the pharmacokinetic studies with adults mean increases in blood pressure of a few

mmHg were frequently observed post dosing. Mean pulse also tended to increase, although in study 103 the greatest increase in mean pulse was seen at 24 hours post dosing.

In study 104, a single dose bioequivalence trial comparing bioavailability of 3X10 mg SLI 381 to 1X30 mg SLI 381 in children with ADHD, mean systolic blood pressure in the post dosing observation period increased by a much as 16 mmHg, with smaller increases in mean diastolic blood pressure, and increases in mean pulse of up to 12 bpm.

8.5.4 Electrocardiograms

No ECG tracings were obtained in study 201. In study 301, subjects had ECGs recorded at baseline and at the end of the study. The following table lists mean changes from baseline for ECG parameters in study 301.

ECG parameter	Placebo mean change	SLI 381 mean change
PR interval (msec)	2.5	-0.3*
QRS interval (msec)	0.2	1.1
Heart rate (bpm)	-1.0	0.3
QTc interval (msec)	2.5	2.1

*p-value = 0.01

There were treatment emergent ECG abnormalities of various types reported in 37 SLI 381 treated patients; however, the sponsor states that all ECG abnormalities were considered clinically insignificant although some were referred to a cardiologist for a second reading. Two subjects (13-01 and 12-25) had premature atrial systoles on drug; a cardiologist deemed the finding in the first subject harmless, and a repeat ECG on the second subject was normal, although it was not clear if that was performed in follow up after the study. A variety of ECG abnormalities were reported in the interim report for the ongoing open label study 302, including Wolff-Parkinson-White syndrome in one subject and junctional rhythm in two subjects. However, no patients discontinued SLI 381 because of an ECG abnormality.

8.5.5 Other safety topics

There have been no reported overdosages with SLI 381. Shire correctly points out in their proposed labeling that in the event of an overdose the treating physician should be mindful of the drug's extended release profile.

Literature review: The sponsor's clinical literature review (provided in the original submission, volumes 41 and 42) did not appear to disclose any new information specifically relevant to SLI 381.

Demographic subgroups: In studies 201 and 301 combined, among subjects receiving

SLI 381, loss of appetite and nausea were more common in boys, and dyspepsia was more common in girls; however, the sponsor did not compare the relative risks for these events between boys and girls. Similarly, among subjects receiving SLI 381, insomnia was more common among Caucasians, while abdominal pain, loss of appetite, anxiety, emotional lability, and nervousness were more frequent among non-Caucasians, but here again the sponsor did not analyze these data in terms of differences in relative risk by ethnic origin.

8.6 Adequacy of safety assessment: The safety methodology was generally adequate. An analysis of weight and height, especially in the long term trial, would have been helpful. Also, the analysis of laboratory abnormalities could have been improved by selecting criterion values for significant abnormalities, and then determining the number of such abnormalities that were treatment emergent. The same comment applies to the vital sign analysis. Finally, more discussion could have been provided regarding the qualitatively abnormal ECG readings, which were simply listed in the report; presumably none were considered particularly concerning from a clinical standpoint.

8.7 Overall conclusions about safety

This is the first large clinical trial dataset available in some time for an amphetamine drug product. Overall the safety profile appears consistent with what would be expected for a sympathomimetic psychostimulant. Weight loss and anorexia were two of the the most frequent adverse reactions, which is not surprising for a drug product that was originally marketed for weight loss. The psychostimulant effects of amphetamine were reflected in the incidence of emotional lability, insomnia and nervousness. Although the findings were not entirely consistent across trials, it is evident that the drug can raise heart rate and blood pressure. There did not appear to be any findings of concern with respect to laboratory or ECG parameters.

The sponsor should provide clarification regarding the abnormalities in serum calcium that were reported in study 301. The sponsor should also provide more information on the two subjects in study 301 who developed premature atrial systoles during treatment with SLI 381.

9.0 Overall Conclusions and Recommendations

This drug product is approvable in my opinion. My suggestions for labeling are attached to this review.

Andrew D. Mosholder, M.D.
Medical Officer, HFD-120

Cc: Laughren, Wheelous, Mosholder

Number of Pages Redacted 13 pages

❖❖❖

Draft Labeling
(not releasable

REVIEW AND EVALUATION OF CLINICAL DATA

NDA 21-303
SPONSOR: SHIRE
DRUG: ADDERALL XR
MATERIAL SUBMITTED: RESPONSE TO APPROVABLE LETTER
DATE SUBMITTED: 8-13-01, 8-14-01, 8-22-01

Review of individual submissions

August 13, 2001

This submission includes the worldwide regulatory update, some CMC information, Shire's agreement to conduct Phase IV bioavailability and juvenile animal studies, and the clinical safety update. (The approvable letter did not request a worldwide literature update).

Worldwide regulatory update: Adderall XR is not marketed in any country. A New Drug Submission is pending in [redacted]

Safety Update: The cutoff date for new safety data in this safety update was 4-30-01. The new safety data comes entirely from the ongoing open label study (302); the total number of subjects in study 302 for which safety data is available is now 516. There is also one ongoing open label study for which no data is yet available; this protocol was submitted to [redacted]

As of the cutoff date of 4-30-01, the total number of subjects exposed to either single or multiple doses was 685, an increase of 42 subjects since the previous safety update. Of these 685 subjects, 595 were children with ADHD participating in safety/efficacy trials, 70 were adult subjects in clinical pharmacology trials, and 20 were children with ADHD in a single dose pharmacokinetic trial.

Duration of exposure: The numbers of patients receiving Adderall XR by duration of treatment is shown below. (Information on duration of exposure by dosage was not available for a large number of these subjects who were in the open label study.) A total of 260 subjects received Adderall XR for over 12 months.

Duration of treatment	Number of subjects
≤2 mo	122
3-4 mo	52
5-6 mo	40
7-8 mo	24
9-10 mo	19
11-12 mo	78
13 mo	186
≥ 14 mo	74

Safety data

Serious adverse events: There have been no deaths in Adderall XR clinical trials. Since the previous safety update there has been one additional serious adverse event experienced by a patient receiving Adderall XR: Subject 41-10 in study 302, an 8-year old girl, was admitted to a psychiatric hospital for severe temper outbursts.

Adverse dropouts: The following were adverse dropouts from study 302 that had not been previously reported. There were a total of 12 such adverse dropouts, of which 5 involved weight loss or anorexia.

Study & Patient	Age & Gender	Adverse event leading to dropout
302/05-04	7 m	Acting drugged, not himself
302/07-03	9 m	Insomnia
302/11-25	8 f	Weight loss
302/11-30	7 m	Not gaining weight and decreased appetite
302/13-05	7 m	Weight loss and decreased appetite
302/22-04	? m	Depression
302/31-02	6 f	Weight loss
302/35-01	6 m	Facial tic (positive dechallenge)
302/35-16	9 m	Loss of appetite
302/38-02	10 f	Obsessive compulsive disorder
302/38-13	7 m	Isolated unusual play behavior
302/55-06	7 f	Depression

Common adverse events: There were no new data from placebo-controlled trials in this safety update. For the open label study 302, as of the cutoff date the following were the most frequent adverse events (incidence $\geq$ 10%) reported: decreased appetite, insomnia, headache, abdominal pain, infection, phayringitis.

Clinical Laboratory findings: The sponsor provided an analysis of laboratory findings in the interim study report for Study 302, submitted 8-22-01. For this analysis, the baseline values were those from the last visit of the double blind treatment in study 301. The difficulty with this is that three-fourths of the subjects in study 301 received Adderall XR during double blind treatment. For these subjects the final visit of double blind treatment occurred while they were already receiving Adderall XR, and thus should not be considered a true baseline.

The following mean laboratory values showed statistically significant changes post-baseline (after either 6 or 12 months of therapy): albumin (decreased), alkaline phosphatase (decreased), BUN (decreased), creatinine (increased), gamma-GT (decreased), glucose (decreased), SGPT (decreased), sodium (increased), total bilirubin (increased), total protein (decreased), uric acid (increased), platelet count (increased), hematocrit (increased), RBC count (increased). However, the magnitude of the mean changes was generally small (the largest proportional mean change was for alkaline phosphatase, a mean decrease of over 10%). With respect to outliers, the most notable finding was that 9.4% of the 318 subjects at month 12 had abnormally low uric acid. In addition, 5.0% of subjects had elevated glucose at month 12 and 3.7% had an elevated platelet count. There was no data reported for calcium, despite the fact that the protocol specified that serum calcium would be among the laboratories obtained. It will be recalled that in the double blind study 301, 9.6% of drug treated subjects and 2.9% of placebo treated subjects had end of study calcium values that were abnormally high.

On balance, these data are very difficult to interpret due to the absence of a comparator group and the sponsor's failure to employ a drug-free baseline for the analyses.

Vital signs: With respect to mean changes in vital sign parameters, there were modest increases from baseline in blood pressure and pulse at various timepoints during open label treatment.

However, as stated above, these data are difficult to interpret because the baseline values to which the on treatment values were compared were not always obtained prior to Adderall XR treatment.

Electrocardiogram data: ECGs were obtained at the end of double blind treatment and at month 12 (or upon discontinuation). With respect to mean changes in ECG parameters, there was a statistically significant increase in QRS duration of 6 msec at month 12. There were a large number of ECG abnormalities of various types reported (a total of 191 at either baseline or month 12), but no subjects discontinued treatment due to any of these abnormalities. As already stated, the sponsor failed to analyze these data relative to a drug-free baseline, making interpretation difficult.

August 22, 2001

This submission is the interim study report for Study 302. Please refer to the description of data from this trial above.

August 14, 2001

This submission contains a discussion of statistical issues pertaining to Study 201, additional analyses of blood pressure data in studies 201 and 301, additional CMC information and a labeling counter-proposal.

Study 201: The statistical issues involved were discussed at an internal meeting 9-14-01. The consensus of the clinical and statistical review teams was that the statistical methodology was not rigorous enough for inclusion of the results in the drug's label. Please refer to the statistical review for details.

Vital Sign data: In study 201, blood pressure was measured pre-dose, and at 1.5 hours, 4.5 hours and 7.5 hours post-dose. The sponsor provided an analysis in this submission showing the mean blood pressure values for each dose group and placebo, using the mean of all post-dose values. The mean change averaged across dose groups for systolic blood pressure was +2.9 mmHg compared to –2.7 mmHg for placebo. For diastolic blood pressure the mean change for all doses was –0.5 mm Hg compared to –1.9 mm Hg for placebo. Using the least squares mean the drug-placebo differences are smaller.

At our request, on 10-1-01 Shire submitted an analysis of mean changes in blood pressure and pulse for each timepoint in study 201, and mean maximum post-dose blood pressure and pulse. Again, there was little evidence for increased pulse or blood pressure with Adderall XR and in some instances the mean values for placebo were actually higher than for drug.

With respect to outliers for blood pressure and pulse, the sponsor provided the following data from study 301. For systolic blood pressure, the percentage of patients having a value > 118 mm Hg was 7.3% for Adderall XR and 8.2% for placebo. For diastolic blood pressure, the percentage of patients having a value > 80 mm Hg was 1.1% for drug and 0.5% for placebo. For pulse, the percentage of patients having a value > 107 bpm was 4.6% for drug and 4.8% for placebo. Thus there did not appear to be an association of outlier values with drug treatment.

Reviewer comment: Shire confirmed that all vital sign readings were obtained after recess, and this may be the explanation for the apparent lack of effect of amphetamine on these vital sign parameters. Physical activity would be expected to increase pulse and blood pressure, and thus

might obscure drug-placebo differences. I recommend omitting the vital sign data obtained in study 201 from the labeling, because of this methodological concern.

Conclusions and recommendations:

1. There are no safety findings in the response to the approvable letter that would preclude approval of this drug product.

2. The sponsor should provide an analysis of vital signs, ECG parameters, and clinical laboratory parameters for study 302 using baseline values obtained prior to double blind treatment in trial 301 as the baseline for analysis. This would provide a comparison of pre-drug to on-drug values for these safety parameters. The sponsor should also provide data on serum calcium values in study 302, or explain why these data are not available.

Andrew D. Mosholder, M.D.
Medical Officer, HFD-120

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

/s/

Andy Mosholder
10/5/01 04:35:37 PM
MEDICAL OFFICER

Thomas Laughren
10/6/01 02:12:18 PM
MEDICAL OFFICER
I agree that this NDA can now be approved.--TPL