CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-303

CHEMISTRY REVIEW(S)

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

13 page(s) of revised draft labeling has been redacted from this portion of the review.

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
7/24/01 02:21:23 PM
MEDICAL OFFICER

Thomas Laughren
7/28/01 12:16:17 PM
MEDICAL OFFICER
I agree that this NDA is approvable; see memo to file for more detaile
d comments.--TPL

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS, HFD-120
REVIEW OF CHEMISTRY, MANUFACTURING, AND CONTROLS

NDA 21-303 CHEM REVIEW: #1 REVIEW DATE: 10/24/2000

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	10/3/2000	10/3/2000	10/10/2000
18 mo. Stability data	03/30/01		
Response to inquiry	06/19/01		

NAME AND ADDRESS OF APPLICANT
Shire Laboratories Inc.

1505 East Gude Drive
Rockville, Maryland 20850

DRUG PRODUCT NAME
Proprietary: Adderall-XR
Non proprietary/USAN: Amphetamine sulfate USA/USN, amphetamine aspartate, dextroamphetamine sulfate USP/USAN, dextroamphetamine saccharate
Code Name/Number: SLI 381
Chem. Type/Ther. Class: 3S

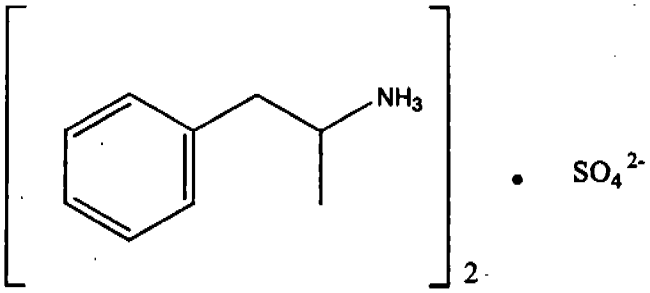
PHARMACOLOGICAL CATEGORY/INDICATION: 1) Treatment of ADHD 2) Treatment of narcolepsey
DOSAGE FORM: Capsules
STRENGTHS: 10 mg, 20 mg, and 30 mg
ROUTE OF ADMINISTRATION: Oral
DISPENSED: x Rx ___OTC
SPECIAL PRODUCTS: ___Yes x No

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA

Active Pharmaceutical Ingredient	Chemical Name	CAS Number
Amphetamine sulfate, USP	(±)-α-Methylphenylamine sulfate	60-13-9
Dextroamphetamine sulfate, USP	(+)-α-Methylphenylamine sulfate	617-48-8
Amphetamine aspartate	(±)-α-Methylphenylamine aspartate	51-63-8
Dextroamphetamine saccharate	(+)-α-Methylphenylamine saccharate	87-73-0

CAS for free amphetamine base is 300-62-9

Dextroamphetamine sulfate USP
Molecular formula: $(C_9H_{13}N)_2.H_2SO_4$
Molecular Weight: 368.50
CAS # 617-48-8



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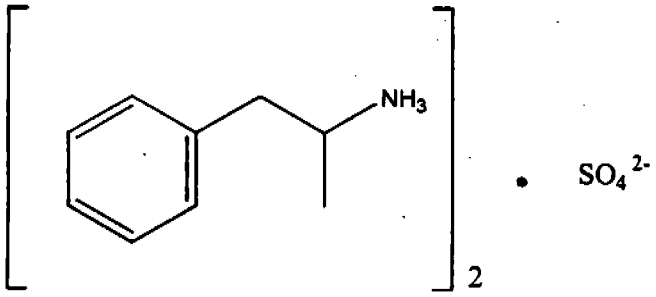

Trade name for immediate release products with this mixed salt combination is ADDERALL.

Chemical Name	Molecular Formula	Molecular Weight
Amphetamine sulfate, USP	$(C_9H_{13}N)_2.H_2SO_4$	368.50
Dextroamphetamine sulfate, USP	$(C_9H_{13}N)_2.H_2SO_4$	368.50

Amphetamine aspartate	$(C_9H_{13}N)_2.C_4H_7NO_4.H_2O$	286.33
Dextroamphetamine saccharate	$(C_9H_{13}N)_2.C_6H_{10}O_8$	480.56

Comments and Recommendation:

This NDA describes a modified-release formulation of previously approved Adderall immediate release dosage form. The sponsor has satisfactorily addressed CMC concerns raised by chemistry reviewer. However, CGMP violations were found at the manufacturing site [redacted] Until the time compliance issues (CGMP) are resolved, this NDA is non-approvable.

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS, HFD-120
REVIEW OF CHEMISTRY, MANUFACTURING, AND CONTROLS

NDA 21-303 CHEM REVIEW: #1 REVIEW DATE: 10/24/2000

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNEDDATE/ACTION
ORIGINAL	10/3/2000	10/3/2000	10/10/2000

NAME AND ADDRESS OF APPLICANT

Shire Laboratories Inc.
1505 East Gude Drive
Rockville, Maryland 20850

DRUG PRODUCT NAME

Proprietary: Amphetamine sulfate USA/USN, amphetamine aspartate, dextroamphetamine sulfate USP/USAN, dextroamphetamine saccharate

Non proprietary/USAN:
Code Name/Number: SLI 381
Chem. Type/Ther. Class: 3S

PHARMACOLOGICAL CATEGORY/INDICATION: 1) Treatment of ADHD 2) Treatment of narcolepsey
DOSAGE FORM: Capsules
STRENGTHS: 10 mg, 20 mg, 30 mg
ROUTE OF ADMINISTRATION: Oral
DISPENSED: x Rx ___OTC
SPECIAL PRODUCTS: ___Yes x No

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA

Active Pharmaceutical Ingradient	Chemical Name	CAS Number
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Dextroamphetamine sulfate, USP	(+)-α-Methylphenylamine sulfate	617-48-8
Amphetamine aspartate	(±)-α-Methylphenylamine aspartate	51-63-8
Dextroamphetamine saccharate	(+)-α-Methylphenylamine saccharate	87-73-0

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Dextroamphetamine saccharate	$(C_9H_{13}N_2)_2.C_6H_{10}O_8$	480.56

SPECIFICATIONS		
Test	Method	Specifications
Appearance		
Identification A		
Identification B		
Loss on Drying		
Specific Rotation (USP Test Dextroamphetamine)		
Residue on Ignition		
Organic Volatile Impurities		
Residual Solvents		
Chromatographic Purity		
Assay		

STABILITY STUDIES: The sponsor has conducted stability studies for the [redacted] conditions for the first 12 months for the three primary stability batches of each finished product strength. The results showed that the drug product appearance, average content, and dissolution properties were virtually unchanged over this period. There were no apparent trends in these results. There were no degradant peaks. Moisture results showed no significant change over time. Microbial limit results showed no significant microorganism growth for the product.

The stability studies were also conducted at [redacted] condition through six months period. The results demonstrate that the product appearance, average content, and dissolution were essentially unchanged over the test period. There were no degradant peaks. Moisture results showed no significant change over time. Microbial limit results showed no significant microorganism growth for the product.

Proposed Expiration Period: Sponsor is requesting the assignment of a 24-month expiration date period for the product. In support of the requested 24-month expiry period Shire has provided a 12- mo of satisfactory primary stability data at [redacted] storage condition. Shire also commits to provide 18 months stability update for the primary stability lots at the [redacted] storage condition approximately six months after submission of this NDA.

Quantitative Composition:

The theoretical composition in weight percent of each component in SLI 381 Immediate-Release and Delayed-Release Tablets is given in the table below. The actual percentages of each component in the formulation differ slightly from the theoretical percentages due to losses of the dispersion components during the fluidized bed drug layering, enteric coating and final coating procedures.

Component	IR Pellets Weight Percent	DR Pellets Weight Percent
Amphetamine Aspartate		
Amphetamine Sulfate, USP		
Dextroamphetamine Saccharate		
Dextroamphetamine Sulfate, USP		
Hydroxypropylmethyl Cellulose, USP (Methocel E% Premium LV)		
Sugar Sphere 30/35 Mesh, NF		
Methacrylic Acid Copolymer Dispersion, NF (Eudragit L30D-55)		
Triethylcitrate, NF		
Talc, USP		
Opadry Beige, (YS-1-17274-A)		
Total	100	100

APPEARS THIS WAY
ON ORIGINAL

Theoretical Milligram/Capsule of Components in SLI 381 Capsules, 10 mg, 20 mg, and 30 mg

Component	10 mg (mg/capsule)	20 mg (mg/capsule)	30 mg (mg/capsule)
Amphetamine Aspartate			
Amphetamine Sulfate, USP			
Dextroamphetamine Saccharate			
Dextroamphetamine Sulfate, USP			
Hydroxypropylmethyl Cellulose, USP (Methocel E% Premium LV)			
Sugar Sphere 30/35 Mesh, NF			
Methacrylic Acid Copolymer Dispersion, NF (Eudragit L30D-55)			
Triethylcitrate, NF			
Talc, USP			
Opadry Beige, (YS-1-17274-A)			
Hard Gelatin Capsule			
Total	155.8	280.9	407.2

COMMENTS: This NDA is fileable for CMC.

APPEARS THIS WAY
ON ORIGINAL