CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-303/S-001

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

M E M O R A N D U M

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

DATE: February 25, 2002

FROM: Thomas P. Laughren, M.D.
Team Leader, Psychiatric Drug Products
Division of Neuropharmacological Drug Products
HFD-120

SUBJECT: Approvable action for NDA 21-303/S-001, involving new capsule strengths (5, 15, & 25 mg) for Adderall XR (mixed amphetamine salts)

TO: NDA 21-303/S-001
[Note: This should be filed with the 10-26-01 original submission.]

Adderall XR is currently available in 10, 20, and 30 mg capsule strengths. This supplement provides 3 intermediate strengths, presumably for greater dosing flexibility.

Since the 15 and 25 mg strengths have the same delayed and immediate release beads, in the same proportion, as in the marketed formulations, there was no need for bioequivalence (BE) trials for these strengths. However, the 5 mg strength has a lower content of drug substance in the immediate release beads, and thus, required a BE study. Study 381.106 was conducted, comparing 4X5 vs Adderall XR 20 mg. The results of this study have been reviewed by Hong Zhao, Ph.D., from OCPB, and she concluded that BE has been established. In addition, each of the new strengths were compared to the 20 mg biobatch, with regard to dissolution, using the approved method, and were judged to be similar by Dr. Zhao. Dr. Zhao has recommended a common dissolution method for all six strengths.

This supplement has also been reviewed by Christy John, Ph.D., from the chemistry group, and he has concluded that the new strengths meet all the regulatory specifications as approved in the original NDA.

Finally, Andrew Mosholder, M.D., from the clinical group, has reviewed this supplement. He noted that the safety profile, namely slight increases in HR and BP, is as expected for this product. He did recommend a slight modification to the D&A section of labeling, i.e., a recommendation for starting doses and incremental increases in 5 or 10 mg steps for the XR, as is currently recommended for the IR. This is entirely rational, and in keeping with the sponsor's stated goal in providing these new strengths.

Conclusion: All three review disciplines have concluded that this application is approvable, and I agree. Thus, I recommend that we issue the attached approvable letter, with our recommendations for common dissolution specifications and for the labeling changes recommended.

cc:
Orig NDA 21-303/S-001
HFD-120/DivFile
HFD-120/TLaughren/RKatz/AMosholder/AHomonnay

DOC: NDA21303.01

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/s/

Thomas Laughren
2/25/02 03:04:57 PM
MEDICAL OFFICER

M E M O R A N D U M

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

DATE: May 14, 2002

FROM: Thomas P. Laughren, M.D.
Team Leader, Psychiatric Drug Products
Division of Neuropharmacological Drug Products
HFD-120

SUBJECT: Approval action for NDA 21-303/S-001, involving new capsule strengths (5, 15, & 25 mg) for Adderall XR (mixed amphetamine salts)

TO: NDA 21-303/S-001
[Note: This should be filed with the 2-27-02 response to our 2-26-02 approvable letter.]

Adderall XR is currently available in 10, 20, and 30 mg capsule strengths. This supplement provides 3 intermediate strengths, presumably for greater dosing flexibility.

In our 2-26-02 approvable letter, we asked for a labeling change, a commitment to submit draft container labels when available, and adoption of a particular dissolution method and specifications.
In their 2-27-02 response, Shire noted that they had already submitted draft container labels and agreed to our proposed dissolution method and specifications.

The one remaining issue was our request that they modify the Dosage and Administration section to recommend 5 or 10 mg qd as the starting dose in children ≥ 6, and to recommend dosage increments of 5 mg or 10 mg. Their original labeling had proposed 10 mg as the starting dose and dosage increments of —

The sponsor agreed to dosage increments of 5 mg or 10 mg, but not with a 5 mg starting dose. They argued that they have not studied the 5 mg dose.

The basis for our recommendation for a 5 or 10 mg starting dose was as follows:
-Current labeling for Adderall IR recommends a starting dose of 5 mg qd or bid for children ≥ 6.
-The plasma concentration time curves for the IR and XR formulations are not dramatically different.

Dr. Mosholder has again argued that the labeling should recommend 5 or 10 mg qd as the starting dose in children ≥ 6. However, I think it is hard to rebut their argument that they have no efficacy data at 5 mg. Since we have not until now objected to the current Adderall XR labeling that recommends 10 mg as the starting dose, I don't think we can reasonable force them to adopt a 5 mg recommendation, especially since they support their argument by noting the lack of data from an adequate and well controlled trial, a position that we usually take. Thus, I am inclined to accept their labeling proposal.

Conclusion: In my view, this NDA can now be approved. Thus, I recommend that we issue the attached approval letter, with their most recent labeling proposal.

cc:
Orig NDA 21-303/S-001
HFD-120/DivFile
HFD-120/TLaughren/RKatz/AMosholder/AHomonnay

DOC: NDA21303.01

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/s/

Thomas Laughren
5/14/02 03:11:32 PM
MEDICAL OFFICER

MEMORANDUM

DATE: February 25, 2002

FROM: Director
Division of Neuropharmacological Drug Products/HFD-120

TO: File, NDA 21-303/S-001

SUBJECT: Action Memo for NDA 21-303/S-001, for the introduction of 3 new dosage strengths (5, 15, and 25 mg) of Adderall XR

NDA 21-303/S-001, for the introduction of 3 new dosage strengths (5, 15, and 25 mg) of Adderall XR, was submitted by Shire Pharmaceutical Development, Inc., on 10/26/01. Adderall XR is currently approved in 10, 20, and 30 mg strengths, and the sponsor proposes that the new strengths will make more flexible dosing possible.

The primary data submitted to support the new strengths consisted of dissolution and CMC data, in addition to a bioequivalence study in which 4 of the 5 mg strengths were compared to a single 20 mg Adderall XR capsule.

The application has been reviewed by Dr. Hong Zhao, Office of Clinical Pharmacology and Biopharmaceutics (review dated 2/11/02), Dr. Christy John, chemist (review dated 2/22/02), Dr. Andrew Mosholder, medical reviewer (review dated 1/2/02), and Dr. Thomas Laughren, Psychiatric Drugs Team Leader (memo dated 2/25/02).

The review team concludes that the application is approvable, and I agree (in particular, 4x5 mg XR are bioequivalent to 20 mg XR). I have only one point that I believe needs further clarification.

Dr. Mosholder recommends that the dosing recommendations for some children 6 years of age and older be amended to state that the starting dose should be 5 mg or 10 mg once a day (as well as making subsequent increments 5 mg or 10 mg; the sponsor had proposed only 10 mg once a day as the starting dose, and, indeed, the 5 mg XR strength would be unnecessary if it would not be indicated for initiation of therapy, because all other 5 mg increments between 10 and 30 mg could be achieved with the proposed 15 and 25 mg strengths). Dr. Mosholder recommends the 5 mg XR dose as a potential starting dose based on 1) the fact that current labeling for Adderall IR recommends starting with 5 mg once or twice a day, and 2) it is rational to start with the lowest dose that might be effective. To my reading, the IR label implies that, at least in some children, a dose of 5 mg once (or twice) a day may be effective.

Similarly, I believe that Dr. Mosholder's recommendation also implies that a dose of Adderall XR given as 5 mg once a day may be effective. Unfortunately, we have no empirical evidence that this is true (the study on which approval of Adderall XR was based studied 10 mg as the lowest dose).

However, I believe that Dr. Mosholder's recommendation may stand.

In particular, based on the absorption pattern of the XR in general, a single 5 mg XR dose should result in a plasma-time concentration curve reasonably similar to that resulting from a single 5 mg IR capsule. Inspection, for example, of the curves resulting from a single 20 mg XR capsule and 2, 10 mg IR capsules given BID (see current XR labeling) suggests that a single 10 mg XR capsule would yield plasma levels not importantly different from a single 10 mg IR capsule. This finding, coupled with the fact that 4, 5 mg XR capsules are equivalent to a 20 mg XR capsule, strongly suggests that a single 5 mg XR capsule should yield plasma levels reasonably close to those resulting from a single 5 mg IR capsule. Since a single 5 mg IR capsule is already recommended in IR labeling as an appropriate starting dose (and, as noted above, the label implies that this may be effective in some patients), I believe it is reasonable to recommend that prescribers initiate treatment with a single 5 mg (or 10 mg) XR capsule in children 6 years of age and older. While I recognize that we do not have definitive (either clinical or bioequivalence) evidence that 5 mg XR is effective, the argument elaborated above is sufficient, in my view, to recommend this as a potential starting dose. While the proposed labeling does imply that this dose may be effective in some patients, the language also clearly states that the dose should be increased to achieve an appropriate clinical response if necessary. Finally, I completely agree with Dr. Mosholder that the labeling should recommend subsequent dosing *increments* of ¯ngs.

For these reasons, I will issue the attached Approvable letter.

Russell Katz, M.D.

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/s/

Russell Katz
2/26/02 08:19:56 AM
MEDICAL OFFICER

RMO REVIEW OF NDA FPL

NDA: 21-303

Supplement: S-001(FA)

Sponsor: Shire Laboratories, Inc.

Product Name: Adderall XR™ CII (extended release capsule—mixed salts of a single-entity amphetamine product)

Submission Date: August 1, 2002

Receipt Date: August 1, 2002

Background: NDA 21-303/S-001 was approved on May 22, 2002 which provides for three additional strengths: 5mg, 15mg and 25mg capsules. Shire submitted the FPL on August 1, 2002 in response to the Division's May 22, 2002 approval letter.

Material Reviewed:

- FPL for Approved Supplement S-001 / August 1, 2002
- Approval letter with the labeling / May 22, 2002

CONCLUSIONS & RECOMMENDATIONS:

I did the line by line comparison of the FPL to the enclosed labeling of May 22, 2002 approval letter and found them to be identical. Therefore, an acknowledge & retain letter may be issued.

_____
Melaine Shin, R.Ph. (for Anna Marie Homonnay)
Regulatory Management Officer

_____
Robbin Nighswander, R.Ph.
Supervisory Regulatory Health Project Manager

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/s/

Melaine Shin
9/13/02 03:01:41 PM
CSO

Robbin Nighswander
10/4/02 02:12:49 PM
CSO

MEMORANDUM OF TELECON

DATE: May 22, 2002

APPLICATION NUMBER: NDA 21-303/S-001

BETWEEN:

Name: Ms. Debbie Aleknavage
Phone: (240) 453-6446
Representing: Shire Pharmaceuticals

AND

Name: Anna Marie H. Weikel, Regulatory Health Project Manager
Division of Neuropharmacological Drug Products, HFD-120

SUBJECT: FDA Recommended Revision to Labeling

I spoke with Ms. Aleknavage this morning regarding the following FDA proposed addition to DOSAGE AND ADMINISTRATION which was discussed with Shire on May 20, 2002:

"When in the judgement of the clinician a lower initial dose is appropriate, patients may begin treatment with 5 mg once daily in the morning."

She said that Shire has agreed to this addition to the labeling.

Anna Marie H. Weikel, RPh
Regulatory Health Project Manager

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/s/

Anna-Marie Homonnay
5/22/02 09:22:34 AM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-303/S-001

PRIOR APPROVAL SUPPLEMENT

Shire Pharmaceutical Development, Inc.
Attention: Raj Kishore, Ph.D., Senior Director, Regulatory Affairs
1901 Research Boulevard Suite 500
Rockville, MD 20850

Dear Dr. Kishore:

We have received your supplemental drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Adderall XR™ CII (extended-release capsule—Mixed Salts of Single-Entity Amphetamine Product)

NDA Number: 21-303

Supplement number: 001

Date of supplement: October 26, 2001

Date of receipt: October 26, 2001

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on December 25, 2001 in accordance with 21 CFR 314.101(a).

All communications concerning this supplement should be addressed as follows:

U.S. Postal Service:
Center for Drug Evaluation and Research
Division of Neuropharmacological Drug Products, HFD-120
Attention: Division Document Room, 4008
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Neuropharmacological Drug Products, HFD-120
Attention: Division Document Room, 4008
1451 Rockville Pike
Rockville, Maryland 20852-1420

If you have any questions, call Anna Marie Homonnay, R.Ph., Regulatory Project Manager, at (301) 594-5535.

Sincerely yours,

Robert H. Seevers, Ph.D.
Chemistry Team Leader
Psychiatric Drugs for the
Division of Neuropharmacological Drug Products
HFD-120
DNDC 1, Office of New Drug Chemistry
Center for Drug Evaluation and Research

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/s/

Robert H. Seevers
10/31/01 03:09:27 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-303\S-001

Shire Laboratories, Inc.
Attention: Rick Lilley, Ph.D
Senior Vice President, Regulatory Affairs
1901 Research Blvd., Suite 500
Rockville, MD 20850

Dear Dr. Lilley:

We acknowledge receipt of your August 1, 2002 submission containing final printed labeling in response to our May 22, 2002 letter approving your supplemental new drug application for Adderall XR™ (Mixed Salts of a Single-Entity Amphetamine Product) Extended-release Capsules.

We have reviewed the labeling that you submitted in accordance with our May 22, 2002 letter and we find it acceptable.

If you have any questions, call Ms. Anna Marie Homonnay, R.Ph., Regulatory Health Project Manager, at 301-594-5535.

Sincerely,

{See appended electronic signature page}

Russell Katz, M.D.
Director
Division of Neuropharmacological Drug Products
Office of Drug Evaluation ODE I
Center for Drug Evaluation and Research

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/s/

Russell Katz

10/21/02 04:09:56 PM