CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

11-522/S-030

MEDICAL REVIEW

MEMORANDUM

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

DATE: November 8, 2002

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

SUBJECT: Recommendation for approval action for NDA 11-522/S-030, for a new formulation for the currently approved tablet strengths for Adderall.

TO: File NDA 11-522/S-030
[Note: This memo should be filed with the 7-8-02 response to our 3-20-02 approvable letter.]

This supplement provides for a new formulation for the existing 7 tablet strengths of Adderall immediate release, i.e., 5, 7.5, 10, 12.5, 15, 20, and 30 mg. The stated goal of the new formulation is to "improve product stability and optimize the new manufacturing process at a new manufacturing site." This supplement was originally reviewed by (1) Wen-Hwei Chou, Pharm.D., Ph.D., from OCPB, (2) Christy John, Ph.D., from chemistry, and (3) Andrew Mosholder, M.D., from the psychopharmacology group. Drs. Chou and Mosholder have reviewed the 7-8-02 response, as has Thomas Oliver, Ph.D., from chemistry.

CMC:
-There were no CMC issues in the approvable letter, and, in fact, the original CMC recommendation had been for approval. This submission included a change in batch size for the 5 mg tablet. There were no other changes. The drug product manufacturing site was found acceptable 3-19-02, and a final update on the two other sites resulted in an acceptability rating 11-5-02. Thus, this application can be approved from a CMC standpoint.

Biopharmaceutics:
-The approvable letter expressed several concerns regarding biopharmaceutics issues:

(1) a request to update labeling with general information regarding the PK of Adderall, from literature or other sources:

-Response: The sponsor proposed several labeling changes in response to this request, however, we have decided to review these separately, along with more substantial changes to labeling proposed in the 3-14-02 amendment (see "Labeling" below).

(2) a request to add to labeling descriptive information about the PK studies that support these new formulations:
-Response: The sponsor accepted the proposed text for this paragraph, with minor modifications that were acceptable to OCPB.

(3) a request to address the finding of numerous plasma samples falling outside of the range of values defined by the bioanalytical method:
-Response: OCPB has concluded that the sponsor has adequately addressed this question.

Clinical:
-The only clinical question in the approvable letter was to ask for clarification of the term in How Supplied, and this issue was addressed. Thus, this application can be approved from a clinical standpoint.

Labeling Issues:
-During the course of the review of this supplement, the sponsor submitted an amendment (3-14-02) which, according to the cover letter for that submission, included verbatim language from the recently approved Adderall XR labeling in order to update the Adderall labeling. In fact, we referenced that amendment in our 3-20-02 approvable letter, noting that additional labeling changes would be needed as well. In particular, we asked for the information noted in items 1 and 2 under Biopharmaceutics (above) to be added as well. We assumed at the time, based on the language in the cover letter, that the changes in the 3-14-02 amendment were verbatim changes we had already approved for Adderall XR. We have only recently discovered that the 3-14-02 amendment contains language that has been substantially altered and requires review. Thus, we have decided that the best administrative solution at this point is to issue an approval letter with the sponsor's originally proposed labeling (11-20-01), with the only addition being a paragraph describing pharmacokinetic information pertinent to this new formulaion. We have reached agreement with the sponsor on this labeling and on this solution. Thus, they will subsequently submit a supplement with the labeling changes submitted in the 3-14-02 amendment, along with a detailed explanation of the source of these changes and rationales for any new information that is being introduced. During the course of the review of this supplement we can address other changes that have been proposed by our OCPB reviewers, i.e., regarding class issues.

Recommendation: I recommend that we issue an approval letter, with the agreed upon final labeling.

cc:
Orig NDA 11-522/S-030
HFD-120/DivFile
HFD-120/TLaughren

DOC: NDA11522.02

REVIEW AND EVALUATION OF CLINICAL DATA

NDA 11-522
SPONSOR: SHIRE
DRUG: ADDERALL (AMPHETAMINE SALTS)
MATERIAL SUBMITTED: RESPONSE TO 3-20-02 APPROVABLE LETTER FOR CMC SUPPLEMENT
DATE SUBMITTED: 7-8-02
DATE RECEIVED: 7-8-02
PDUFA GOAL DATE: 11-8-02

This CMC supplement provides for new formulations of all seven marketed strengths of Adderall immediate release tablets (5, 7.5, 10, 12.5, 15, 20 and 30 mg). There was one clinical question in the approvable letter, regarding the sponsor's proposed replacement of the term
in the How Supplied section of labeling.

In this submission, Shire explains that the term is preferable according to the American Pharmaceutical Association Tablet Design Criteria. The 5 mg tablets do have two interrupted score lines, set at right angles to each other, and can be broken in half to allow the 2.5 mg dosage recommended for initiation of treatment in children under 6 years of age.

Reviewer Comment: This is an adequate reponse to the inquiry in the approvable letter. There are no other remaining clinical issues. The proposed changes to the Clinical Pharmacology section of labeling seem reasonable from a clinical standpoint, but they should be reviewed by OCPB.

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

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/s/

Andy Mosholder
10/8/02 05:03:31 PM
MEDICAL OFFICER

Thomas Laughren
10/9/02 12:30:01 PM
MEDICAL OFFICER

REVIEW AND EVALUATION OF CLINICAL DATA

NDA 11-522
SPONSOR: SHIRE
DRUG: ADDERALL (AMPHETAMINE)
MATERIAL SUBMITTED: CMC SUPPLEMENT FOR REFORMULATION OF EXISTING TABLET STRENGTHS
DATE SUBMITTED: 11-20-01
DATE RECEIVED: 11-20-01
USER FEE DUE DATE: 3-20-02

This supplement provides for a new formulation of the existing tablet strengths of Adderall. The color of the 5 mg tablet will change from blue to white. The description of the other tablets in the "How Supplied" section is somewhat different from that in the current labeling, and I was unable to tell if the appearance of the other tablets will actually be different. In particular, instead of describing the tablets as double-scored, they will now be described as However, as with the existing tablets, the mg strength will be indicated on the tablet.

In support of this supplement, the sponsor conducted two in vivo bioequivalence studies. Study 371.101 was a single dose two way crossover study comparing bioavailability of the new 30 mg tablet to the marketed 30 mg tablet; eighteen healthy adult volunteers participated. Study 371.102 was a single dose two way crossover study comparing the new and the marketed 10 mg tablets; eighteen healthy adult volunteers participated. Please refer to the OCPB review by Dr. Wen-Hwei Chou of OCPB.

In study 371.101, which tested 30 mg doses, there were no unique adverse events with the new formulation. Of interest, the majority of subjects receiving 30 mg as either formulation reported "euphoria," consistent with the high abuse potential of amphetamine. With respect to vital sign changes, the mean increase from baseline in systolic blood pressure was greatest at 2 hours after dosing, with a change of +16 mmHg for the new formulation and +14 mmHg for the marketed formulation. Similarly, the maximum mean change in diastolic blood pressure also occurred at 2 hours (+8 mmHg for the new formulation and +7 mmHg for the marketed tablet). The mean change in pulse was +9 bpm for the new formulation and +10 bpm for the marketed tablet, both at 4 hours after dosing. Although post-dose EKGs were obtained, only individual data listings were provided (no analysis of mean parameters was performed).

In study 371.102, 10 mg doses were tested. One subject dropped out of the study after the first dose for "personal reasons." There were no unique adverse events reported with the new formulation; in contrast to the 30 mg study, no subjects reported euphoria. The mean changes in vital sign parameters were somewhat less than with the 30 mg dose. Systolic blood pressure increased by 6-8 mm Hg, diastolic blood pressure increased by 5-6 mmHg, and pulse increased by 5-7 bpm.

Conclusions and recommendations: There were no new safety issues for Adderall disclosed by the bioequivalence studies. Prior to approval, the sponsor should clarify their use of the term ' with respect to the new tablets, and in particular whether the 5 mg strength can be broken in half, which is required to achieve the recommended starting dose of 2.5 mg for very young children.

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

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/s/

Andy Mosholder
3/18/02 05:24:09 PM
MEDICAL OFFICER

Thomas Laughren
3/19/02 10:21:45 AM
MEDICAL OFFICER
I agree that this supplement is approvable; see memo to file for more detailed comments.--TPL

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: March 19, 2002

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

SUBJECT: Recommendation for approvable action for NDA 11-522/S-030, for a new formulation for the currently approved tablet strengths for Adderall.

TO: File NDA 11-522/S-030
[Note: This memo should be filed with the 11-20-01original submission.

This supplement provides for a new formulation for the existing 7 tablet strengths of Adderall immediate release, i.e., 5, 7.5, 10, 12.5, 15, 20, and 30 mg. The stated goal of the new formulation is to "improve product stability and optimize the new manufacturing process at a new manufacturing site." This supplement has been reviewed by (1) Wen-Hwei Chou, Pharm.D., Ph.D., from OCPB, (2) Christy John, Ph.D., from chemistry, and (3) Andrew Mosholder, M.D., from the psychopharmacology group.

The sponsor conducted 2 in vivo bioequivalence studies . Study 371.101 compared single doses of the new 30 mg tablet with the marketed 30 mg tablet, and Study 371.102 compared single doses of the new 10 mg tablet with the marketed 10 mg tablet. These studies were required due to the multiple changes in manufacturing site, equipment, and process. An accepted approach, and the one used here, is to show BE at the highest strength and do dissolution testing for the lower strengths to support biowaivers. The 7 strengths were divided into 2 groups based on tablet compression methods, i.e., 5, 7.5, and 10 as group I, and 12.5, 15, 20, and 30 mg as group II. BE was shown for the 30 mg and 10 mg strengths within each of these groups, and dissolution testing was provided to support biowaivers for the remaining strengths. Dr. Chou and OCPB agreed that this standard has been met with the submitted data. However, they do have several comments for the sponsor, including (1) a request to update labeling with general information regarding the PK of Adderall, from literature or other sources, (2) a request to add to labeling descriptive information about the PK studies that support these new formulations, and (3) a request to address the finding of numerous plasma samples falling outside of the range of values defined by the bioanalytical method. Nevertheless, they found the supplement acceptable, and referred to these requests as "postapproval."

The manufacturing, controls, and stability information provided for this supplement were found to be acceptable, and as of this morning, the Office of Compliance indicated acceptance of the new manufacturing site. Thus, the chemistry group has recommended approval of the supplement.

Dr. Mosholder examined the safety findings from the 2 BE studies, and concluded that there were no new safety findings that would impact on the labeling of this product. He did note, however, one issue worthy of some discussion. The new tablets are referred to as having while the currently marketed tablets are referred to as double-scored. It is important to be able to divide the 5 mg tablet, in particular, for titration with very young children. Thus, it needs to be clarified what the terms mean.

It should be noted that we just received (3-14-02) an amendment to this supplement including numerous additional changes to the labeling, essentially incorporating a number of additions to the Adderall XR labeling to the Adderall labeling. The letter will note that this amendment could not be reviewed during this cycle, but will be reviewed along with their response to the approvable letter.
Recommendation: I recommend that we issue an approvable letter, however, without labeling. The letter should indicate that we will review the recently amended labeling once they make the additional requested changes.

cc:
Orig NDA 11-522/S-030
HFD-120/DivFile
HFD-120/TLaughren

DOC: NDA11522.01

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/s/

Thomas Laughren
3/19/02 11:34:21 AM
MEDICAL OFFICER