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RESEARCH**

*APPLICATION NUMBER:*  
**21-303/S-001**

**MEDICAL REVIEW**

## REVIEW AND EVALUATION OF CLINICAL DATA

NDA 21-303

SPONSOR: SHIRE

DRUG: ADDERALL XR

MATERIAL SUBMITTED: RESPONSE TO APPROVABLE LETTER FOR SUPPLEMENT S-001  
(NEW 5 MG, 15 MG, AND 25 MG DOSAGE STRENGTHS)

DATE SUBMITTED: 2-27-02

DATE RECEIVED:

This submission is Shire's response to our approvable letter of 2-26-02. Shire states in the submission that they have already submitted the draft container labels and have already adopted the requested dissolution method. There is one unresolved clinical issue, however, that concerns the new language in the Dosage and Administration section. Please refer to the statements shown below.

Requested language in the 2-26-02 approvable letter:

"In children with ADHD who are 6 years of age and older and are either starting treatment for the first time or switching from another medication, start with 5 mg or 10 mg once daily in the morning; daily dosage may be raised in increments of 5 mg or 10 mg at weekly intervals."

Shire counter-proposal 2-27-02: "In children with ADHD who are 6 years of age and older and are either starting treatment for the first time or switching from another medication, start with ~~5 mg~~ or 10 mg once daily in the morning; daily dosage may be raised in increments of 5 mg or 10 mg at weekly intervals."

[Current immediate-release Adderall labeling: "...In children 6 years of age and older, start with 5 mg once or twice daily; daily dosage may be raised in increments of 5 mg at weekly intervals until optimal response is obtained..."]

Shire does not wish to indicate in the labeling that 5mg daily may be the starting dose, because the lowest starting dose in the Adderall XR clinical trials was 10 mg.

Reviewer comment: We discussed this very issue prior to sending the approvable letter; please refer to Dr. Katz's memo dated 2-25-02. I would make the following observations: (1) the Adderall XR clinical trial development program was an abbreviated program simply designed to show activity of the new formulation, given that the drug substance is already marketed for the indication; it was not designed to ascertain the lowest appropriate starting dose. (2) In clinical practice, amphetamine is usually assumed to be roughly twice as potent as methylphenidate, for which the recommended starting dose is 10 mg/day (5 mg twice daily). (3) For this indication, the dosage can always be titrated upwards if there is an insufficient clinical response, which will be immediately obvious to parents, teachers, and physicians. (4) The current Adderall immediate release labeling includes 5 mg as a possible initial daily dose, and as Dr. Katz stated in his memo, the differences in the plasma concentration-time curve between IR and XR are not dramatic.

I recommend retaining the language we proposed in our approvable letter.

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

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/s/

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Andy Mosholder  
3/18/02 01:11:45 PM  
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Thomas Laughren  
5/14/02 03:04:31 PM  
MEDICAL OFFICER  
I agree that this NDA can now be approved;  
see memo to file for more detailed comments.--TPL

## REVIEW AND EVALUATION OF CLINICAL DATA

NDA 21-303

SPONSOR: SHIRE

DRUG: ADDERALL XR (AMPHETAMINE)

MATERIAL SUBMITTED: SUPPLEMENT FOR NEW CAPSULE STRENGTHS (SCM-001)

DATE SUBMITTED: 10-26-01

DATE RECEIVED: 10-26-01

Adderall XR, the extended-release formulation of Adderall, is marketed in 10, 20 and 30 mg capsule strengths. This supplement provides for the additional strengths of 5, 15, and 25 mg.

The 15 and 25 mg capsules are made with the same delayed and immediate release beads that are in the marketed capsule strengths. Therefore, there was no clinical study to establish the bioavailability of these strengths.

The 5 mg capsule, ~~is not marketed in the United States.~~ Because of the change in the formulation, Shire conducted an in-vivo bioavailability study to support bioequivalence of the 5 mg capsule.

The bioequivalence trial (designated Study 381.106) was an open-label, single dose crossover trial involving twenty patients aged 6-12 years. The children received 20 mg Adderall XR prior to breakfast, administered as four 5 mg capsules and one 20 mg capsule.

This study will be reviewed by OCPB. For reference, the pharmacokinetic results are shown here (means and standard deviations). According to Shire's analysis, these results meet the statistical requirements for establishing bioequivalence.

Amphetamine isomer	Dosage	Cmax (ng/ml)	Tmax (hr)	AUC <sub>∞</sub> (hrX ng/ml)	T ½ (hr)
D	4X5 mg	52 (13)	4.7 (2.3)	873 (184)	7.9 (1.0)
D	20 mg	52 (15)	4.5 (1.7)	815 (174)	8.0 (1.3)
L	4X5 mg	17 (4)	5.0 (2.4)	307 (69)	9.0 (1.1)
L	20 mg	16 (5)	4.9 (1.9)	269 (59)	9.1 (1.6)

With respect to safety findings from this trial, hypertension and tachycardia were the most commonly noted adverse events, occurring in 18 and 12 of the 20 subjects, respectively. Most of the subjects with these events experienced them following both dosages. The criteria for hypertension were as follows: systolic bp  $\geq 130$  mm Hg and/or diastolic bp  $\geq 85$  mm Hg, and increase  $> 20\%$  from baseline. The criteria for tachycardia were pulse  $\geq 120$  bpm and increase  $> 20\%$  from baseline.

Conclusions and recommendations: The vital sign findings in the bioequivalence study confirm the well-known effects of amphetamine on pulse and blood pressure. From a clinical standpoint there is no objection to approval of the additional capsule strengths.

Labeling: The sponsor has proposed changes to the Description and How Supplied sections to reflect the new capsule strengths. I recommend one additional change, as follows.

Adderall XR has the following instructions under Dosage and Administration: "In children with ADHD who are 6 years of age and older and are either starting treatment for the first time or switching from another medication, start with 10 mg once daily in the morning; daily dosage may be raised in increments of 10 mg at weekly intervals. Dosage should be individualized according to the needs and response of the patient. Amphetamines should be administered at the lowest effective dosage. The maximum recommended dose is 30 mg/day; doses greater than 30 mg/day of ADDERALL XR™ have not been studied."

Immediate-release Adderall has slightly different instructions: "...In children 6 years of age and older, start with 5 mg once or twice daily; daily dosage may be raised in increments of 5 mg at weekly intervals until optimal response is obtained..."

With the addition of the 5, 15, and 25 mg capsules, physicians will have greater flexibility in titrating patients, and I suggest that the labeling be amended to reflect this. I propose the following additions (shown in italics): "In children with ADHD who are 6 years of age and older and are either starting treatment for the first time or switching from another medication, start with ~~5~~ 10 mg once daily in the morning; daily dosage may be raised in increments of *5 mg or 10 mg* at weekly intervals."

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

Cc: Laughren, Mosholder, Homonnay

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Andy Mosholder  
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