# CENTER FOR DRUG EVALUATION AND RESEARCH

## Approval Package for:

## *APPLICATION NUMBER:*
# 21-303

***Trade Name:*** Adderall XR Capsule

***Generic Name:*** mixed salt of a single entity amphetamine product

***Sponsor:*** Shire Laboratories, Inc.

***Approval Date:*** October 11, 2001

***Indications:*** Provides for the use of Adderall XR Capsule for the treatment of Attention Deficit Hyperactivity Disorder.

# CENTER FOR DRUG EVALUATION AND RESEARCH

## *APPLICATION NUMBER:*
## 21-303

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| Tentative Approval Letter | | | | |
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| Final Printed Labeling | X | | | |
| Medical Review(s) | | | | |
| Chemistry Review(s) | X | | | |
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| Pharmacology Review(s) | X | | | |
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# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

**21-303**

# APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

NDA 21303

Shire Laboratories, Inc
Attention: Tami Martin
Vice President, Regulatory Affairs
1550 East Gude Drive
Rockville, MD 20850

Dear Ms. Martin:

Please refer to your new drug application (NDA) dated October 3, 2000, received October 3, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Adderall XR (mixed salt of a single entity amphetamine product) Capsule.

We acknowledge receipt of your submissions dated:

| | | |
|---|---|---|
| August 13, 2001 | August 14, 2001 | August 22, 2001 |
| August 29, 2001 | September 25, 2001 | October 2, 2001 |
| October 3, 2001 | | |

Your submission of August 14, 2001 constituted a complete response to our August 3, 2001 action letter.

This new drug application provides for the use of Adderall XR (mixed salt of a single entity amphetamine product) Capsule for the treatment of Attention Deficit Hyperactivity Disorder.

We have completed the review of this application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon enclosed labeling text. Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit the copies of final printed labeling (FPL) electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA* (January 1999). Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved NDA 21303." Approval of this submission by FDA is not required before the labeling is used.

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632). We note that you have not fulfilled the requirements of 21 CFR 314.55 (or 601.27). We are deferring submission of your pediatric studies for the under six years of age group. However, in the interim, please submit your pediatric drug development plans within 120 days from the date of this letter unless you believe a waiver is appropriate. Within approximately 120 days of receipt of your pediatric drug development plan, we will review your plan and notify you of its adequacy.

If you believe that this drug qualifies for a waiver of the pediatric study requirement, you should submit a request for a waiver with supporting information and documentation in accordance with the provisions of 21 CFR 314.55 within 60 days from the date of this letter. We will notify you within 120 days of receipt of your response whether a waiver is granted. If a waiver is not granted, we will ask you to submit your pediatric drug development plans within 120 days from the date of denial of the waiver.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the *Guidance for Industry on Qualifying for Pediatric Exclusivity* (available on our web site at www.fda.gov/cder/pediatric) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request" (PPSR) in addition to your plans for pediatric drug development described above. We recommend that you submit a Proposed Pediatric Study Request within 120 days from the date of this letter. If you are unable to meet this time frame but are interested in pediatric exclusivity, please notify the division in writing. FDA generally will not accept studies submitted to an NDA before issuance of a Written Request as responsive to a Written Request. Sponsors should obtain a Written Request before submitting pediatric studies to an NDA. If you do not submit a PPSR or indicate that you are interested in pediatric exclusivity, we will review your pediatric drug development plan and notify you of its adequacy. Please note that satisfaction of the requirements in 21 CFR 314.55 alone may not qualify you for pediatric exclusivity. FDA does not necessarily ask a sponsor to complete the same scope of studies to qualify for pediatric exclusivity as it does to fulfill the requirements of the pediatric rule.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

As a Phase 4 commitment please submit a patient information package for our review.

If you have any questions, call Ms. Anna Marie Homonnay, R.Ph., Regulatory Project Manager, at (301) 5945535.

Sincerely,

*{See appended electronic signature page}*

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

Enclosure

# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

**21-303**

# APPROVABLE LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-303

Shire Laboratories, Inc
Attention: Tami Martin
Vice President, Regulatory Affairs
1550 East Gude Drive
Rockville, MD 20850

Dear Ms. Martin:

Please refer to your new drug application (NDA) dated October 3, 2000, received October 3, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Adderall XR (mixed salt of a single entity amphetamine product) capsules.

We acknowledge receipt of your submissions dated:

| | | |
|---|---|---|
| December 18, 2000 | February 6, 20001 | February 13, 2001 |
| February 20, 2001 | March 30, 2001 | April 23, 2001 |
| May 17, 2001 | June 19, 200 | June 22, 2001 |
| June 29, 2001 | | |

This new drug application provides for the use of Adderall XR Capsules for the treatment of attention deficit disorder.

We have completed the review of this application, as amended, and it is approvable. Before this application may be approved, however, it will be necessary for you to address the following:

**Labeling Issues**

Accompanying this letter as an attachment, is our labeling proposal, including explanations, for ADDERALL XR. We ask that you adopt this labeling for approval. If you would like to further discuss this labeling proposal, a teleconference may be arranged through the division project manager.

**Worldwide Regulatory Status Update**

Please provide any new information on the worldwide regulatory status of ADDERALL XR, including the status of all actions either taken or pending before any foreign regulatory authorities.

**Clinical Pharmacology / Biopharmaceutics Issues**

1. Please adopt the following dissolution method and specifications for all three strengths (10, 20 and 30 mg) of Adderall XR capsules:

**Apparatus:** [redacted]

**Media:** [redacted]

**Specifications:** [redacted]

**Clinical / Statistical Issues**

While your analyses of the [redacted] attention and deportment scales in Study 201 are suggestive of an overall effect of Adderall XR, we have concerns about the design and analysis of this study that lead us to conclude that it cannot be described in labeling. A fundamental problem is that no clear objective or primary hypotheses were specified. The time course analysis had been designated as secondary in the original protocol and was only changed to a primary analysis two months after study completion. Furthermore, time course was never adequately defined. Neither the original protocol nor the subsequent analysis plan stated clearly what outcome would be required to consider the study positive overall. In addition, there are concerns regarding the study design and analysis that you have not adequately addressed: (1) The design provided for a five-way crossover, with the randomized sequences generated from the Latin-Square. Because five-way crossover studies are rarely used as study designs for efficacy trials, please provide a justification for the use of this design, as well as for the specific way you have chosen to analyze the trial. In addition, the analysis of multiple outcomes (e.g., several time points) per treatment period in cross-over studies, in general, is potentially problematic; please discuss this issue. An additionalcommon problem with the crossover design is that the study result will be difficult to interpret when there are missing data, and this problem is further complicated by missing data at certain time points in this study. You have not discussed the impact of missing data on the study result. (2) Regarding the analysis, you have not provided a detailed description of the mixed effect model that you used. You will need to provide the references that validate the use of the proposed model for this type of design. In addition, the many sources of multiplicity, e.g., multiple endpoints and sub-scales, multiple doses, and multiple testing times, are not adequately addressed in the analysis plan. Thus, until these various concerns have been adequately addressed, it will not be possible to refer to the results of this trial in labeling.

**CMC**

During recent inspections of the manufacturing facilities for your NDA, a number of deficiencies were noted and conveyed to you or your suppliers by the investigator. Satisfactory inspections will be required before this application may be approved.

**Safety Update**

Under 21 CFR 314.50(d)(5)(vi)(*b*), we request that you update your NDA by submitting all safety information you now have regarding your new drug. The safety update should include data from all nonclinical and clinical studies of the drug under consideration regardless of indication, dosage form,

or dose level.

1. Describe in detail any significant changes or findings in the safety profile.

2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

   - Present new safety data from the studies for the proposed indication using the same format as the original NDA submission.

   - Present tabulations of the new safety data combined with the original NDA data.

   - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.

   - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

3. Present a retabulation of the reasons for premature study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.

4. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.

5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.

6. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

7. Provide English translations of current approved foreign labeling not previously submitted.

**Phase 4 Commitments**

Please commit to providing information regarding the bioavailability of amphetamine from both Adderall IR tablets and Adderall XR capsules relative to an optimally available dosage form, such as a solution, and the metabolic fate of amphetamine for labeling purposes. These data should be submitted within one year of the approval date of this application.

You have previously committed to performing a juvenile animal study. The protocol for this study should be submitted as soon as possible for Division concurrence.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

If you have any questions, call Anna Marie Homonnay, R.Ph., Regulatory 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 I
Center for Drug Evaluation and Research

Enclosure: