

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

11-522/S-030

APPROVAL LETTER



NDA 11-522/SCF-030

Shire Pharmaceutical Development Inc.
Attention: Rick Lilley, Ph.D.
Senior Vice President, Regulatory Affairs
1901 Research Boulevard
Rockville, MD 20850

Dear Dr. Lilley:

Please refer to your supplemental new drug application dated November 20, 2001, received November 20, 2001, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for ADDERALL® (Mixed Salts of a Single-Entity Amphetamine Product) Tablets, 5 mg, 7.5 mg, 10 mg, 12.5 mg, 15 mg, 20 mg and 30 mg Tablets.

We acknowledge receipt of your amendment dated July 8, 2002.

This chemistry, manufacturing, and controls (CMC) supplement provides for reformulation of the tablets and a new manufacturing site.

We further refer to the November 7, 2002, teleconference between you and members of this Division during which the labeling changes proposed in the March 14, 2002, amendment and regulatory options were discussed.

Finally we refer to the November 8, 2002, telephone conversation between Ms. Catherine Symington of the Regulatory Affairs Department and Ms. Anna Marie H. Weikel of this Division during which the text of the approved labeling below was agreed upon.

We have completed the review of this supplemental 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 labeling text dated November 20, 2001, with the agreed upon additions below to the 'Pharmacokinetics' section. These labeling additions specifically pertain to the formulation changes that are being made in this supplement. Accordingly, this supplemental application is approved effective on the date of this letter.

‘Pharmacokinetics

ADDERALL® tablets contain d-amphetamine and l-amphetamine salts in the ratio of 3:1. Following administration of a single dose 10 or 30 mg of ADDERALL® to healthy volunteers under fasted conditions, peak plasma concentrations occurred approximately 3 hours post-dose for both d-amphetamine and l-amphetamine. The mean elimination half-life ($t_{1/2}$) for d-amphetamine was shorter than the $t_{1/2}$ of the l-isomer (9.77-11 hours vs. 11.5-13.8 hours). The PK parameters (C_{max} , AUC_{0-inf}) of d-and l-amphetamine increased approximately from 10 mg to 30 mg indicating dose-proportional pharmacokinetics.’

‘The effect of food on the bioavailability of ADDERALL® has not been studied.’

The final printed labeling (FPL) must be identical to the submitted draft labeling and the agreed upon changes to the labeling above.

Please submit 20 paper copies of the FPL as soon as it is available, in no case more than 30 days after it is printed to each application. Please individually mount ten of the copies on heavy-weight paper or similar material. Alternatively, you may submit the FPL electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDAs* (January 1999). For administrative purposes, this submission should be designated "FPL for approved supplement NDA 11-522/S-030". Approval of this submission by FDA is not required before the labeling is used.

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

If you should have any questions, please call, Ms. Anna Marie H. Weikel, R.Ph., Regulatory Affairs Manager, at (301) 594-5535.

Sincerely,

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