# CENTER FOR DRUG EVALUATION AND RESEARCH

**Application Number** 21-121

## APPROVAL LETTER

NDA 21-121

Alza Corporation
Attention: Jane Wissel
Senior Vice President, Operations
950 Page Mill Road
P.O. Box 10950
Palo Alto, CA 94303-0802

Letter Issued 8/1/00

Dear Ms. Wissel:

Please refer to your new drug application dated July 15, 1999, received July 19, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for CONCERTA™ (methylphenidate HCl) Extended-release Tablets.

We acknowledge receipt of your submission dated June 1, 2000, which constituted a complete response to our May 18, 2000, approvable letter.

We also acknowledge receipt of your amendments dated June 14, 19, and 28; and July 7, 2000 (revised draft labeling).

We further note your additional communications dated July 9 and 12, 2000 (revised draft labeling).

This new drug application provides for the use of CONCERTA™ Extended-release Tablets for the treatment of attention deficit 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 enclosed draft labeling. Accordingly, the application is approved effective on the date of this letter.

**LABELING**

Accompanying this letter as an attachment is the final labeling for CONCERTA™ Extended-release Tablets. We note your communications of July 9 and 12, 2000, and the telephone conference of July 31, 2000, between members of this Division and representatives of Alza, through which agreement was reached on the content of this labeling.

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

Please submit 20 copies of the FPL as soon as it is available, in no case 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 21-121." Approval of this submission by FDA is not required before the labeling is used.

**BIOPHARMACEUTICS**

The following in vitro dissolution specifications have been approved for the 18 mg and 36 mg strengths:

| | Specification of label claim(%range) |
|---|---|
| Time Point | Specification |
| at 1 h | (b)(4)-------- -------- |
| at 4 h | ---------- |
| at 10 h | -------- |
| release rate | ---------- |

The *in vitro* testing is performed with USP Type VII dissolution apparatus with oral extended release tablet holder (spring holder) in pH 3 water with a fixed agitation rate of 30 cycles per minute.

**CHEMISTRY**

Expiration Date

We have approved an expiration date of 24 months for both the 18 mg and 36 mg tablets.

Methods Validation

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; however, we trust that you will continue to work with the Agency to accomplish this. Please submit three copies of the following analytical methods for a new methods validation package for an FDA laboratory:

1. b)(4)----------¥----------
2. ----------¥----------
3. ----------¥----------
4. ----------¥----------
5. ----------¥----------

**PHASE IV COMMITMENT**

We also remind you of your Phase 4 commitment specified in your June 1, 2000, response to our approvable letter as listed below:

> Submission of a draft protocol for a preliminary juvenile rat study for assessing toxicity and pharmacokinetic parameters within 90 days post-approval followed by the completion of a definitive study in the juvenile rat with particular emphasis on neurobehavioral and reproductive parameters within 20 months of agreement on its design.

Protocols, data, and final reports should be submitted to this NDA as correspondence. In addition, under 21 CFR 314.82(b)(2)(vii), we request that you include a status summary of your commitment in your annual report to this NDA. For administrative purposes, all submissions relating to this Phase 4 commitment should be clearly designated "Phase 4 Commitments."

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81. In addition, as part of your post-marketing surveillance program, we request that you submit all adverse event reports involving GI obstruction, bezoar formation, and GI perforation as 15-day alert reports.

We also refer to your pediatric waiver request under 21 CFR 314.55(c). We have reviewed the information you have submitted and agree that a waiver is justified for CONCERTA™ for the treatment of attention deficit disorder for the under six years of age group. Accordingly a waiver for pediatric studies is granted at this time.

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 send one copy to the Division of Neuropharmacological Drug Products and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-40
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

If you should have any questions, contact Anna M. Homonnay-Weikel, R.Ph., Regulatory Project 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

Enclosure