CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-208

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-208

Organon Inc.
Attention: Albert P. Mayo
Director, Regulatory Affairs
375 Mt. Pleasant Avenue
West Orange, NJ 07052

Dear Mr. Mayo:

Please refer to your new drug application (NDA) dated December 30, 1999, received December 30, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Remeron SolTab (mirtazapine) Orally Disintegrating 15 mg, 30 mg, and 45 mg Tablets.

We acknowledge receipt of your submissions dated November 13, and 22, 2000. Your submission of November 13, 2000 constituted a complete response to our October 30, 2000 action letter.

This new drug application provides for the use of Remeron SolTab Orally Disintegrating Tablets for the treatment of depression.

Reference is also made to a telephone conversation dated December 21, 2000, between Ms. Carol Shichman, of your firm, and Mr. Paul David, of this Agency, in which Organon agreed to the attached labeling for Remeron SolTab.

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 20 paper 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. 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 NDA 21-208." Approval of this submission by FDA is not required before the labeling is used.

Additionally, we note your agreement, conveyed in your November 13, 2000 resubmission, to adopt the following dissolution method and specification for all strengths of the Remeron SolTab (mirtazapine) Orally Disintegrating 15 mg, 30 mg, and 45 mg Tablets:

Apparatus: USP Apparatus 2 (Paddle) at 50 rpm
Medium: 900 mL 0.1 N HCl at 37°C±0.5°C
Specification: [redacted]

We additionally note your agreement, conveyed in the aforementioned telephone conversation dated December 21, 2000, to make identical labeling changes to the **PRECAUTIONS-Use in Patients with Concomitant Illness, ADVERSE REACTIONS-ECG Changes**, and **ADVERSE REACTIONS-Other Adverse Events Observed During Postmarketing Evaluation of Remeron** sections to the Remeron labeling, NDA 20-415, in the form of a "Changes Being Effected" supplemental application.

Please note that even though the adverse events "torsades de pointes" and "ventricular arrhythmias" are currently in the labeling under the **ADVERSE REACTIONS-Other Adverse Events Observed During Postmarketing Evaluation of Remeron** section, we are requiring that you continue to submit these adverse events as Postmarketing 15-day Alert Reports to our Office of Postmarketing Drug Risk Assessment (OPDRA).

The 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.

Additionally, we note that you did not address the pediatric rule in your submission. However, the Agency has issued a pediatric written request letter dated April 28, 1999, to the Remeron NDA 20-415 informing you of the types of studies required to develop mirtazapine in pediatric depression (age range 7 to 17 years old). We request that you submit your pediatric development plan for assessing pediatric safety and effectiveness. If this pediatric development plan was previously submitted to NDA 20-415, you may simply submit a letter cross referencing that submission. Your pediatric development plan should also include a time frame when you intend to submit the results of these studies to the Agency.

Please submit one market package of the drug product when it is available.

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 have any questions, call Paul David, R.Ph., Regulatory Project Manager, at (301) 594-5530.

Sincerely,

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 21-208

APPROVABLE LETTER

Food and Drug Administration
Rockville MD 20857

NDA 21-208

Organon Inc.
Attention: Albert P. Mayo
Director, Regulatory Affairs
375 Mt. Pleasant Avenue
West Orange, New Jersey 07052

OCT 30 2000

Dear Mr. Mayo:

Please refer to your new drug application (NDA) dated December 30, 1999, received December 30, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Remeron SolTab (mirtazapine) Orally Disintegrating 15 mg, 30 mg, and 45 mg Tablets.

We acknowledge receipt of your submissions dated February 17, March 7, April 28, June 13, July 13, July 21, July 27, August 16, August 28, August 30, and October 5, 2000.

We additionally acknowledge receipt of your facsimile transmission dated October 30, 2000, informing the Agency that Organon is formally withdrawing the Organon Inc. Sub Akzona Inc. facility (Establishment #2211109), used as a second site for drug product quality control testing and release, from this new drug application.

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

CLINICAL

1. **Labeling**
   Accompanying this letter (Attachment) is the Agency's proposal for the labeling of Remeron SolTab. This labeling is identical to the most recently approved labeling for Remeron (mirtazapine) tablets (approved in an Agency letter dated August 30, 2000 for NDA 20-415/S-006) except for the highlighted revisions. All references to the Remeron (mirtazapine) tablets have been removed since the labeling for this new dosage form of mirtazapine will be a separate label. The Agency's revisions are based on the following a) labeling changes proposed in your August 30, 2000 submission and your October 13, 2000 e-mail, b) labeling changes requested in Agency letters dated June 26, 1998, and October 6, 1999, and c) labeling revisions discussed in a conference call held on October 17, 2000, between the Agency and representatives from Organon.

2. **Additional Analyses of Cardiac Data**
   We note your commitment made in the aforementioned conference call dated October 17, 2000, to reanalyze your cardiac data using a linear correction for QT interval. Based upon the results of this reanalysis, this may change our proposed labeling and/or we may request that you conduct a Phase 4 clinical pharmacology study to determine if there is a dose-related lengthening of the QT interval associated with mirtazapine.

OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS

We request that you adopt the following dissolution method and specification for all strengths of the Remeron SolTab (mirtazapine) Orally Disintegrating 15 mg, 30 mg, and 45 mg Tablets:

Apparatus: USP Apparatus 2 (Paddle) at 50 rpm
Medium: 900 mL 0.1 N HCl at 37°C±0.5°C
Specification: —

Please submit 20 paper copies of the final printed labeling ten of which are individually mounted 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).

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

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 Paul David, R.Ph., Regulatory Project Manager, at (301) 594-5530.

Sincerely,

/S/

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

Attachment

Number of Pages Redacted 20

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Draft Labeling
(not releasable

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: December 23, 2000

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

SUBJECT: Recommendation for approval action for Remeron SolTab (mirtazapine) 15, 30, and 45 mg strengths

TO: File NDA 21-208
[Note: This memo should be filed with the 11-13-00 response to our 10-30-00 approvable letter.]

Remeron is an approved drug product, for the treatment of depression, currently available in 15, 30, and 45 mg immediate release tablet strengths. This NDA provides for an orally disintegrating dosage form of mirtazapine, with identical strengths to the currently marketed formulation.

We issued an approvable letter for this NDA on 10-30-00, requesting certain labeling changes and the adoption of our proposed dissolution specifications. In part the labeling changes pertained to the new dosage form, however, in addition we had asked Organon to adopt changes regarding QTc prolongation data that we had asked for previously but had not yet been accepted by the sponsor.

Organon accepted our dissolution specifications and all labeling changes pertinent to the new dosage form. However, they did not immediately accept our proposed changes regarding the QTc prolongation data. During a 10-17-00 telcon with the sponsor regarding the QTc prolongation data, we had suggested that they recalculate the QTc prolongation data using a different formula, given that mirtazepine produces a slight increase in heart rate (see my 10-23-00 memo). Organon performed these calculations, and in their view (in 11-13-00 response), the new data suggested that mirtazapine has no important effect on QTc prolongation. In general, we agreed that the effect was now of more questionable clinical significance, however, the effect was not completely eliminated. (See Dr. Mosholder's 12-19-00 review). We proposed revised language that acknowledged a small effect of unknown clinical significance. In the meantime, there were two more reports of TDP in association with Remeron use, however, in both cases, other drugs known to be associated with TDP were also being taken. Thus, there were a total of 4 cases of TDP in association with Remeron use, 3 of which were confounded by other drugs or underlying medical

conditions that made interpretion of mirtazepine's role very difficult. Ultimately, we reached agreement with Organon (on 12-21-00) on labeling that presented all the data, but acknowledged the unknown clinical significance.

Recommendation

Thus, I recommend that we proceed with an approval action at this time, with the mutually agreed upon final labeling.

cc:
Orig NDA 21-208
HFD-120/DivFile
HFD-120/TLaughren/RKatz/AMosholder/PDavid

DOC: NDA21208.02

APPEARS THIS WAY
ON ORIGINAL

/s/

Thomas Laughren
12/23/00 11:39:41 AM
MEDICAL OFFICER

APPEARS THIS WAY
ON ORIGINAL