

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**Application Number 21-208**

**ADMINISTRATIVE DOCUMENTS**  
**CORRESPONDENCE**

## MEMORANDUM

DATE: January 11, 2000

FROM: Division Director  
Division of Neuropharmacological Drug Products/HFD-120

TO: File, NDA 21-208

SUBJECT: Action Memo for NDA 21-208, for the use of Remeron (mirtazipine) SolTab Orally Disintegrating Tablets.

NDA 21-208, for the use of Remeron (mirtazipine) SolTab Orally Disintegrating Tablets, was submitted by Organon, Inc. on 12/30/99. The application was the subject of an Approvable letter dated 10/30/00. In that letter, we asked the sponsor to adopt specific dissolution specifications (which they have done), as well as to further analyze their clinical data for any effects on QT prolongation (preliminary analyses suggested such an effect, but it was felt that an inappropriate correction factor was used to calculate the QTc interval, given the drug's slight effect on increasing heart rate).

The sponsor responded to the Approvable letter with a submission dated 11/13/00. This response included the requested re-analyses, and has been reviewed by Dr. Andrew Mosholder, medical officer (review dated 12/19/00), and Dr. Thomas Laughren, Psychiatric Drugs Team Leader (memo dated 12/23). Both Drs. Laughren and Mosholder recommend that the application be approved with labeling that they have negotiated with the sponsor.

In brief, the sponsor's re-analyses of the QT data suggest that there is a small increase in QTc interval in patients on Remeron compared to placebo patients (mean change from baseline of + 1.6 msec for Remeron patients, and -3.1 for placebo patients). The clinical meaning of this difference (4.7 msec) is unknown, and the absolute change from baseline for the Remeron patients, is, of course, very small. Nonetheless, the review team has negotiated language in the Adverse Reactions section of labeling, in which a section entitled **ECG Changes** describes these changes and states that the clinical meaning of this difference is unknown.

I agree that the labeling as negotiated is adequate. It occurs to me, however, that it may be prudent to ultimately further explore the dose response of any QTc prolonging effect of the drug.

Specifically, it appears that there is still residual concern that Remeron is capable of prolonging the QTc interval. If this is true, it is reasonable to assume at the moment that this effect may be dose/exposure related. As I understand it, however, we have no adequate information about dose response. I note that the

drug is extensively metabolized, with CYP 1A2 apparently being the primary mode of metabolism. In addition, though, 2D6 and 3A4 are involved, apparently to a lesser extent for the parent, and perhaps also for several of the metabolites. It might be important to understand the effects on the metabolism of mirtazipine and/or its metabolites (if there is a QTc prolonging effect, we do not know which circulating species is responsible) of various metabolic inhibitors, and genetic polymorphisms (i.e., poor metabolizers). I recognize that Dr. Zhao, in her review of 9/18/00, suggests that the presence of several primary metabolic pathways is likely to prevent important kinetic effects of the inhibition of any one of these, but I am not sure what the data are about specific contributions of specific P450 enzymes.

For these reasons, I believe that this should be discussed with the review team, and, if necessary, the sponsor should be requested to address this further (I also note that the sponsor has been asked in the past to address the dose response of the effect-if any-on the QTc interval, but they have not specifically responded to that request). This concern, though, will not interfere with my issuance of the Approval letter

Russell Katz, M.D.

CC:  
NDA 21-208  
HFD-120  
HFD-120/Katz/Laughren/Mosholder/David  
HFD-860/Zhao/Baweja

**APPEARS THIS WAY  
ON ORIGINAL**

/s/

-----  
Russell Katz  
1/12/01 07:48:10 AM  
MEDICAL OFFICER

**APPEARS THIS WAY  
ON ORIGINAL**

DAVID

APR 28 1999

NDA 20-415

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

Three Years from  
the Date of This Letter APR 28 2002

Dear Mr. Mayo:

Reference is made to your Proposed Pediatric Study Request dated August 21, 1998 and revised January 25, 1999, submitted under \_\_\_\_\_ for Remeron (mirtazepine) tablets.

We have completed our review of your submission and concluded that your proposed pediatric study request is incomplete.

To obtain needed pediatric information on mirtazapine the Food and Drug Administration (FDA) is hereby making a formal Written Request, pursuant to Section 505A of the Federal Food, Drug, and Cosmetic Act (the Act), that you submit information from the trials in pediatric patients with depression described below.

#### **Background Comments on Pediatric Depression**

Under current regulations [21 CFR 201.57(f)(9)(iv)], a new claim in a pediatric population could be established by extrapolating the effectiveness results of adequate and well controlled studies in adults for the same entity if it were believed that depression was essentially the same disease in adults and children. Under FDAMA (1997), a claim might be based on a single study in pediatric patients along with confirmatory evidence from another source, perhaps adult data for that disorder, an approach considered in the draft guidance document entitled "Guidance for Industry - Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products". This approach too requires some degree of belief that the course of the disease and the effects of the drug are sufficiently similar in the pediatric and adult populations to make data from the adult efficacy studies pertinent to pediatric patients. Unfortunately, in our view there is little reason to assume continuity between adult and pediatric depression and our concern about the extrapolability of adult depression data to pediatric depression is more than theoretical. While we, of course, acknowledge the one published positive report of fluoxetine in pediatric depression (Emslie, et al, 1997), we are concerned about the preponderance of negative studies of antidepressants in pediatric populations. We recognize that all of these negative studies utilized tricyclic antidepressants, and that, in addition, there are other possible explanations for the negative outcomes, e.g., sample size, entry criteria, outcome measures, etc. Nevertheless, these

negative trials (at least 12 in number) lead to a substantial concern about the ability to extrapolate positive antidepressant findings from adult to pediatric patients. Consequently, we believe that a pediatric depression claim for any antidepressant already approved in adult depression would need to be supported by two independent, adequate and well controlled clinical trials in pediatric depression. In addition, a pediatric depression program would need to include pharmacokinetic information and safety information in the relevant pediatric age groups. For pediatric depression, we consider the relevant age groups to include children (ages 7 through 11) and adolescents (ages 12 through 17).

### **Specific Study Requirements for Development Program in Pediatric Depression**

#### **Types of Studies**

Pediatric Efficacy and Safety Studies

Pediatric Pharmacokinetic Study

Pediatric Safety Study

#### **Objective/Rationale**

The overall goal of the development program is to establish the safety and efficacy of the study drug in the treatment of pediatric depression, and to develop other information, e.g., pharmacokinetic, pertinent to using the drug in the pediatric population.

#### **Study Design**

Pediatric Efficacy and Safety Studies

- For the controlled efficacy studies, conduct two randomized, double-blind, parallel group, placebo-controlled acute treatment trial, with a recommended duration of at least 6 to 8 weeks. We recommend that at least one of the two studies should be a fixed dose study including two or more fixed doses of the study drug. You may consider dosing patients on the basis of patient weight. Randomization must be stratified by the two age groups studied. Ideally, a relapse prevention trial would follow from the acute treatment trials, involving the randomization of responders from the acute treatment trials to continuation on either study drug or placebo, with follow-up observation for relapse for a period of 6 months or more. Please note that a relapse prevention trial is not required under this written request.

#### **Pediatric Pharmacokinetic Study**

- A pharmacokinetic study to provide information pertinent to dosing of the study drug in the relevant pediatric population. These data could come from traditional pharmacokinetic studies, or alternatively, from population kinetic approaches applied to controlled efficacy trials or to other safety trials. You should be aware that a guidance document on population pharmacokinetic studies is available under [[www.fda.gov/cder/guidance/1852fnl.pdf](http://www.fda.gov/cder/guidance/1852fnl.pdf)].

**Pediatric Safety Study**

- Safety data should be collected in the controlled efficacy trials. Longer-term safety data should be generated in longer-term open extensions from these trials and/or in separate longer-term open safety studies.

**Age Group in Which Study(ies) will be Performed – All Studies**

Both children (ages 7 to 11) and adolescents (ages 12 to 17) should be equally represented in the samples, and there should be a reasonable distribution of both sexes in these strata.

**Number of Patients to be Studied or Power of Study to be Achieved**

**Pediatric Efficacy and Safety Studies**

- While it is difficult to specify the sample size needed to show a difference between drug and placebo in this population, it should be noted that, in the only published positive antidepressant trial in pediatric depression (Emslie, et al, 1997), there were 48 patients in each of the two treatment arms.

**Pediatric Pharmacokinetic Study**

- A sufficient number of subjects to adequately characterize the pharmacokinetics in the above age groups.

**Pediatric Safety Study**

- A sufficient number of pediatric patients to adequately characterize the safety of mirtazapine at clinically effective doses for a sufficient duration.

**Entry Criteria**

The protocols should include a valid and reliable diagnostic method for recruiting children and adolescents with major depressive disorder.

**Study Endpoints:**

**Pediatric Efficacy and Safety Studies**

- It is essential to identify a single primary outcome for the controlled efficacy trials, and ordinarily this should be change from baseline to endpoint on whatever symptom rating scale you have chosen for your trials.

**Pediatric Pharmacokinetic Study**

- Pharmacokinetic measurements as appropriate.

**Pediatric Safety Study**

- Appropriately frequent standard measures of safety (clinical - including signs and symptoms and laboratory).

**Statistical Information:**

**Pediatric Efficacy and Safety Studies**

- These trials should have a detailed statistical plan. Ordinarily these trials should be designed with at least 80% statistical power to detect a treatment effect of conventional ( $p=0.05$ ) statistical significance.

**Pediatric Pharmacokinetic Study**

- Descriptive analysis of the pharmacokinetic parameters.

**Pediatric Safety Study**

- Descriptive analysis of the safety data.

**Study Evaluations****Pediatric Efficacy and Safety Studies**

- A scale specific to pediatric depression and sensitive to the effects of drug treatment of pediatric depression, e.g., the Children's Depression Rating Scale—Revised, and a global measure, e.g., the Clinical Global Impression (CGI).

**Pediatric Pharmacokinetic Study**

- The pharmacokinetic assessments should be made with respect to the study drug and any metabolites that make substantial contributions to its efficacy and/or toxicity. For the parent and each metabolite followed, the data collected should provide estimates of the pharmacokinetic parameters including AUC, half-life,  $C_{max}$ ,  $t_{max}$ , and apparent oral clearance in pediatric subjects in the relevant age range. You should be aware that a draft guidance document on pediatric pharmacokinetic studies is available under [[www.fda.gov/cder/guidance/index.htm](http://www.fda.gov/cder/guidance/index.htm), under Clinical/Pharmacological (Draft)].

**Pediatric Safety Study**

- Routine safety assessments should include vital signs, weight, clinical laboratory, ECGs, and monitoring for adverse events. Although not a part of this Written Request, we remind you that it may be important to determine the effect of the study drug on the growth and development of pediatric patients, and we encourage you to consider longer-term studies of a year or more to address this question if the acute studies demonstrate antidepressant activity.

**Drug Information**

Use age appropriate formulations in the studies described above. Since the pediatric patient population consists of both children (ages 7 to 11) and adolescents (ages 12 to 17), your marketed solid dosage formulation should be adequate for these studies.

**Drug Concerns**

No specific concerns related to administration to pediatric patients were identified while studying mirtazapine in adults, nor have specific concerns been identified during the postmarketing experience.

**Severe Neutropenia/Agranulocytosis**

In the adult clinical trials for depression, there was an incidence of severe neutropenia or agranulocytosis of roughly 1.1 per 1000 patients. Although not part of this written request, we urge you to consider methods that might help determine if the risk in pediatric patients for such blood dyscrasias is higher, lower, or about the same as in adults. Unless the pediatric risk is considerably higher than for adults, it is unlikely that formal clinical trials will be large enough to provide meaningful incidence data. It may be more appropriate to consider using large postmarketing databases which can be linked to prescriptions, such as HMO or Medicaid databases.

**Labeling That May Result from the Studies**

Results found in the pediatric depression population efficacy, safety, and pharmacokinetic studies could result in the addition to labeling of information pertinent to these studies.

**Format of Reports to be Submitted**

Full study reports or analyses, not previously submitted to the Agency, addressing the issues outlined in this request, with full analysis, assessment, and interpretation.

**Timeframe for Submitting Reports of the Study(ies)**

Reports of the above studies must be submitted to the Agency within 3 years from the date of this letter to be eligible to qualify for pediatric exclusivity extension under Section 505A of the Act. Please remember that pediatric exclusivity extends only existing patent protection or exclusivity that has not expired at the time you submit your reports of studies in response to this Written Request.

Please submit protocols for the above studies to an investigational new drug application (IND) and clearly mark your submission **"PEDIATRIC PROTOCOL SUBMITTED FOR PEDIATRIC EXCLUSIVITY STUDY"** in large font, bolded type at the beginning of the cover letter of the submission. We recommend you seek a written agreement with FDA before developing pediatric studies. Please notify us as soon as possible if you wish to enter into a written agreement by submitting a proposed written agreement. Clearly mark your submission **"PROPOSED WRITTEN AGREEMENT FOR PEDIATRIC STUDIES"** in large font, bolded type at the beginning of the cover letter of the submission.

Reports of the studies should be submitted as a supplement to your approved NDA with the proposed labeling changes you believe would be warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission **"SUBMISSION OF PEDIATRIC STUDY REPORTS – PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED"** in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter. Please also send a copy of the cover letter of your submission, via fax (301-594-0183) or messenger to the Director, Office of Generic Drugs, HFD-600, Metro Park North II, 7500 Standish Place, Rockville, MD 20855-2773.

If you wish to discuss any amendments to this Written Request, please submit proposed changes and the reasons for the proposed changes to your application. Submissions of proposed changes to this request should be clearly marked "PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES" in large font, bolded type at the beginning of the cover letter of the submission. You will be notified in writing if any changes to this Written Request are agreed upon by the Agency.

We hope you will fulfill this pediatric study request. We look forward to working with you on this matter in order to develop additional pediatric information that may produce health benefits to the pediatric population.

If you have any questions, contact Paul A. David, Regulatory Project Manager, at (301) 594-5530.

Sincerely yours,

  
Robert Temple, M.D. 4/28/99  
Director  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

APPEARS THIS WAY  
ON ORIGINAL

cc:

Archival NDA 20-415

HFD-120/division file

HFD-120/PDavid

HFD-120/RKatz/TLaughren/Amosholder/RGlass

HFD-100/RTemple

HFD-600/Office of Generic Drugs

HFD-2/MLumpkin

HFD-104/DMurphy

HFD-6/KRoberts

Drafted by:03/22/99am;rg

Rev:03/29/99tl; 04/02/99rt;04/12/99tl;4/21/99pdit

Final:04/22/99pd

filename: REMERONPES02.DOC

*4-23-99*

*4/22/99 AM 4/22/99*

*IS 4/28/99*

PEDIATRIC WRITTEN REQUEST LETTER  
INFORMATION REQUEST (IR)

APPEARS THIS WAY  
ON ORIGINAL

MODE = MEMORY TRANSMISSION

START=DEC-20 12:27

END=DEC-20 12:29

FILE NO. = 124

STN NO.	COM	ABBR NO.	STATION NAME/TEL.NO.	PAGES	DURATION
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-FDA/DNDP

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Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Drug Evaluation I

**FACSIMILE TRANSMITTAL SHEET**

**DATE: December 20, 2000**

<b>To:</b> Carol B. Shichman	<b>From:</b> Paul David
<b>Company:</b> Organon Inc.	Division of Division of Neuropharmacological Drug Products
<b>Fax number:</b> 973-325-4769	<b>Fax number:</b> (301) 594-2859
<b>Phone number:</b> 973-325-4655	<b>Phone number:</b> (301) 594-5530

**Subject:** Proposed labeling

**Total no. of pages including cover:** 3

**Comments:** See attached.

**Document to be mailed:**       YES       NO

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Attachment

*Labeling  
Approved by  
Organon  
12-21-00  
[Signature]*



Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Drug Evaluation I

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**FACSIMILE TRANSMITTAL SHEET**

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**DATE: December 20, 2000**

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<b>Company:</b> Organon Inc.	Division of Division of Neuropharmacological Drug Products
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<b>Phone number:</b> 973-325-4655	<b>Phone number:</b> (301) 594-5530
<b>Subject:</b> Proposed labeling	

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**Total no. of pages including cover:** 3

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**Comments:** See attached.

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**Document to be mailed:**             YES             NO

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Attachment

[Note: Below is the Agency's labeling counterproposal to your resubmission dated November 13, 2000. Our goal is to obtain labeling agreement at the Team Leader level prior to forwarding the action package to Dr. Katz. The labeling below only includes the sections in which there is disagreement since Organon has previously accepted all of the other labeling revisions conveyed in the Agency approvable letter dated October 30, 2000. Double underline font denotes additions to the labeling, and strikeout font denotes deletions to the labeling. We have included bracketed text to explain the labeling changes. Additionally, please note that we would like to obtain your commitment to submit identical labeling changes in the form of a "Changes Being Effected" supplemental application to the Remeron (mirtazapine) Tablets NDA application, 20-415. ]

## **PRECAUTIONS**

### Use in Patients with Concomitant Illness

[We continue to believe that the statement about a lack of clinically significant ECG abnormalities is too reassuring, and therefore, it should be removed from the labeling.]

Clinical experience with REMERON<sup>®</sup> SolTab<sup>™</sup> in patients with concomitant systemic illness is limited. Accordingly, care is advisable in prescribing mirtazapine for patients with diseases or conditions that affect metabolism or hemodynamic responses.

REMERON<sup>®</sup> SolTab<sup>™</sup> has not been systematically evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or other significant heart disease.

REMERON<sup>®</sup> was associated with significant orthostatic hypotension in early clinical pharmacology trials with normal volunteers. Orthostatic hypotension was infrequently observed in clinical trials with depressed patients. REMERON<sup>®</sup> SolTab<sup>™</sup> should be used with caution in patients with known cardiovascular or cerebrovascular disease that could be exacerbated by hypotension (history of myocardial infarction, angina, or ischemic stroke) and conditions that would predispose patients to hypotension (dehydration, hypovolemia, and treatment with antihypertensive medication).

### **Drug Interactions**

[Based on your recent reanalysis of the QT data, we agree that the data do not warrant this statement, and it can be deleted.]

As with other drugs, the potential for interaction by a variety of mechanisms (e.g., pharmacodynamic, pharmacokinetic inhibition or enhancement, etc.) is a possibility (see

CLINICAL PHARMACOLOGY).

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## ADVERSE REACTIONS

### ECG Changes

[In this section, we believe the best approach is simply to describe the findings.]

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The electrocardiograms for 338 patients who received REMERON<sup>®</sup> and 261 patients who received placebo in 6-week, placebo-controlled trials were analyzed. Prolongation in QTc > 500 msec was not observed among mirtazapine treated patients; mean change in QTc was +1.6 msec for mirtazapine and -3.1 msec for placebo. Mirtazapine was associated with a mean increase in heart rate of 3.4 bpm, compared to 0.8 bpm for placebo. The clinical significance of these changes is unknown.

[We continue to believe that this new subsection should be included in the labeling. Please note, however, that we have also included the disclaimer that these events may have no causal relationship to the drug.]

### Other Adverse Events Observed During Postmarketing Evaluation of REMERON

Adverse events reported since market introduction, which were temporally (but not necessarily causally) related to mirtazapine therapy, include four cases of the ventricular arrhythmia torsades de pointes. In three of the four cases, however, concomitant drugs were implicated. All patients recovered.

APPEARS THIS WAY  
ON ORIGINAL

**Number of Pages**  
**Redacted** 21 pages



Draft Labeling  
(not releasable)

# SUMMARY REPORT

Application: NDA 21208/000  
Stamp: 30-DEC-1999 Regulatory Due: 14-JAN-2001  
Applicant: ORGANON INC  
375 MT PLEASANT AVE  
WEST ORANGE, NJ 07052

Priority: 3S  
Action Goal:  
Brand Name: REMERON  
(MIRTAZAPINE)15/30/45MG TABS  
Established Name:  
Generic Name: MIRTAZAPINE  
Dosage Form: TAB (TABLET)  
Strength: 15MG, 30MG, 45MG

Org Code: 120

District Goal: 31-AUG-2000

FDA Contacts: P. DAVID (HFD-120)  
S. MCLAMORE (HFD-810)  
R. SEEVERS (HFD-120)

301-594-2850 , Project Manager  
301-594-5359 , Review Chemist  
301-594-2850 , Team Leader

*Site received*  
*[Signature]*

## Overall Recommendation:

**WITHHOLD on 27-OCT-2000 by S. FERGUSON (HFD-324) 301-827-0062**

Establishment: 2133845  
CIMA LABORATORIES INC  
1000 VALLEY VIEW ROAD  
EDEN PRARIE, MN 55344

DMF No:  
AADA No:

Profile: TCM OAI Status: NONE  
Last Milestone: OC RECOMMENDATION  
Milestone Date: 10-AUG-2000  
Decision: ACCEPTABLE  
Reason: DISTRICT RECOMMENDATION

Responsibilities: FINISHED DOSAGE  
MANUFACTURER  
FINISHED DOSAGE RELEASE  
TESTER  
FINISHED DOSAGE STABILITY  
TESTER

Establishment: \_\_\_\_\_  
\_\_\_\_\_

DMF No:  
AADA No: 020415

Profile: CSN OAI Status: NONE  
Last Milestone: OC RECOMMENDATION  
Milestone Date: 08-FEB-2000  
Decision: ACCEPTABLE  
Reason: DISTRICT RECOMMENDATION

Responsibilities: \_\_\_\_\_  
\_\_\_\_\_

Establishment: \_\_\_\_\_  
\_\_\_\_\_

DMF No:  
AADA No: 020415

Profile: CSN OAI Status: NONE  
Last Milestone: OC RECOMMENDATION  
Milestone Date: 27-OCT-2000

Responsibilities: \_\_\_\_\_

# SUMMARY REPORT

TESTER

Decision: **ACCEPTABLE**  
Reason: **DISTRICT RECOMMENDATION**

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Establishment:

DMF No:  
AADA No:

Profile: **CRU** OAI Status: **NONE**  
Last Milestone: **OC RECOMMENDATION**  
Milestone Date: **01-AUG-2000**  
Decision: **ACCEPTABLE**  
Reason: **BASED ON PROFILE**

---

Responsibilities: \_\_\_\_\_

Establishment:

DMF No:  
AADA No:

Profile: **CTL** OAI Status: **NONE**  
Last Milestone: **OC RECOMMENDATION**  
Milestone Date: **16-AUG-2000**  
Decision: **ACCEPTABLE**  
Reason: **BASED ON PROFILE**

---

Responsibilities: \_\_\_\_\_

Establishment: **2211109**  
**ORGANON INC SUB AKZONA INC**  
**375 MT PLEASANT AVE**  
**WEST ORANGE, NJ 07052**

DMF No:  
AADA No:

Profile: **CTL** OAI Status: **OAI ALERT**  
Last Milestone: **OC RECOMMENDATION**  
Milestone Date: **27-OCT-2000**  
Decision: **WITHHOLD**  
Reason: **WARNING LETTER ISSUED**

---

Responsibilities: **FINISHED DOSAGE RELEASE**  
**TESTER**

Establishment: **2529406**  
**ORGANON INC SUB AKZONA INC**  
**6350 HEDGEWOOD DR**  
**ALLENTOWN, PA 18103**

DMF No:  
AADA No:

Profile: **TCM** OAI Status: **NONE**

Responsibilities: **FINISHED DOSAGE PACKAGER**

# SUMMARY REPORT

Last Milestone: **OC RECOMMENDATION**  
Milestone Date: **01-FEB-2000**  
Decision: **ACCEPTABLE**  
Reason: **BASED ON PROFILE**

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Establishment: **9610342**  
**ORGANON NV**  
**5340-BH**  
**OSS, , NL**

DMF No:  
AADA No: **020415**

Profile: **CTL**            OAI Status: **NONE**  
Last Milestone: **OC RECOMMENDATION**  
Milestone Date: **25-JUL-2000**  
Decision: **ACCEPTABLE**  
Reason: **BASED ON PROFILE**

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Responsibilities: **DRUG SUBSTANCE OTHER TESTER**  
**DRUG SUBSTANCE RELEASE**  
**TESTER**

**APPEARS THIS WAY  
ON ORIGINAL**

## MEMORANDUM

DATE: October 30, 2000

FROM: Director  
Division of Neuropharmacological Drug Products/HFD-120

TO: File, NDA 21-208

SUBJECT: Action memo for NDA 21-208, for the use of Remeron (mirtazapine) orally disintegrating tablets (15, 30, and 45 mg).

NDA 21-208, for the use of \_\_\_\_\_ (15, 30, and 45 mg), was submitted by Organon, Inc., on 12/30/99. Remeron tablets are approved for the treatment of depression. The current NDA contains a bioequivalence study comparing the performance of the 30 mg orally disintegrating tablet with that of the approved 30 mg tablet, as well as the relevant CMC information.

The data have been reviewed by the CMC, biopharmaceutics, pharmacology, and clinical staff as described by Dr. Thomas Laughren, Psychiatric Drugs Team Leader, in his memo of 10/23/00. Dr. Laughren recommends that the application be considered Approvable; the sponsor needs to do additional work to establish the drug's effect (if any) on the QT interval. Further, largely related to this issue, the labeling will need additional changes.

There is one issue that needs brief description.

The division learned on 10/27/00 (Friday) that the New Jersey FDA District office issued a Warning Letter to the sponsor on 9/19/00 as a result of an inspection of the West Orange, New Jersey manufacturing site. This site was submitted to the NDA as a quality control and release testing site. Dr. Seevers, Chemistry Team Leader, had concluded that some of the deficiencies noted in this letter were sufficiently important that, in his view, the NDA would be considered Not Approvable if the site were kept in the NDA (discussion held with review team on 10/30/00). The sponsor was informed of this in a phone call, and subsequently withdrew this facility from the NDA via a fax submission dated 10/30/00. There is an additional site, in Minnesota, that was already submitted to the NDA and found to be acceptable, that will now perform the quality control and release testing.

Given this, I will issue the attached Approvable letter with the included draft labeling.

^  
/S/

Russell Katz, M.D.

Cc:

NDA 21-208

HFD-120

HFD-120/Katz/Laughren/Mosholder/McLamore/Seevers/David

HFD-860/Zhao/Baweja

**APPEARS THIS WAY  
ON ORIGINAL**

**MEMORANDUM****DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH**

**DATE:** October 23, 2000

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

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

**TO:** File NDA 21-208  
[Note: This memo should be filed with the 12-30-99 original submission.]

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.

This NDA includes the necessary CMC information, the results of a 14-day GI toxicity study in dogs, and the results of a bioequivalence study comparing this new formulation with the currently marketed formulation.

The package includes 2 CMC reviews by Sherita McLamore, Ph.D. recommending approvable actions; these were dated 6-13-00 and 8-16-00, and provided comments that were conveyed to the sponsor. The sponsor has now responded adequately to all comments, and a final review recommending approval is dated 9-11-00. The inspection is also adequate.

The package includes a pharmacology review by Linda Fossom, Ph.D. dated 9-22-00 and also recommending approval of this NDA.

The data from the bioequivalence study and from dissolution testing were reviewed by Hong Zhao, Ph.D. from OCPB, and again, the recommendation in a 9-18-00 review is that the application can be approved; a recommendation for alternative dissolution specifications was included in the review. Ray Baweja, Ph.D. from OCPB also responded, in a 10-17-00 e-mail, to a recommendation from DSI that the BE study not be accepted because of the sponsor's failure to retain study drug samples. Dr. Baweja noted that this finding is irrelevant, given the successful outcome of the BE study and the dissolution testing. I agree.

The currently proposed tradename, i.e., Remeron Soltab, has been deemed to be acceptable by OPDRA, unlike the previously proposed name, ~~\_\_\_\_\_~~

The package also contains a clinical review by Andrew Mosholder, M.D. (8-21-00) from the clinical group. He also recommended that this application is approvable, pending certain changes in labeling.

Several labeling changes were proposed to the sponsor, in a fax dated 10-10-00, including importantly that they include information regarding QTc changes that we had originally requested for the currently marketed tablet in a 10-6-99 letter. The sponsor, in a return e-mail (10-13-00), accepted all of the labeling recommendations except ~~\_\_\_\_\_~~

In a 10-17-00 telcon, we discussed with the sponsor primarily the issue of how best to describe the QTc findings in labeling. The following pertains to our discussions of the QTc findings as proposed in the sponsor's 10-13-00 version of labeling:

-Use in Patients with Concomitant Illness, under Precautions:

~~\_\_\_\_\_~~

~~\_\_\_\_\_~~

-Drug Interactions, under Precautions:

-We were also able to persuade the sponsor of the need to include the statement regarding potential drug interactions in this section rather than under the Concomitant Illness section.

-ECG changes, under Adverse Reactions:

-We agreed to a revised version of the summary of the QTc and heart rate changes, along with a reference to the Other Events section for a mention of 2 spontaneous reports of cases of TDP.

-Other Adverse Events..., under Adverse Reactions:

-We did not reach agreement on how best to describe the 2 cases in question; however, we agreed to discuss their earlier comments on these cases with our consultants in HFD-110.

-One issue that became apparent in the course of these discussions that had not been apparent earlier was that the correction method used for the mirtazapine QT data, i.e., the Bazett square root correction, was likely not appropriate, given the increase in HR seen with this drug, and we all agreed it would be best not to try to reach final agreement on the description of the QT data in labeling until the sponsor had an opportunity to recalculate the QTc data using a more appropriate correction. We subsequently provided the sponsor with our current advice regarding how best to make these corrections. Thus, we were all in agreement with moving toward an approvable rather than an approval action at this time.

**Recommendation**

Thus, I recommend that we proceed with an approvable action at this time, thus giving the sponsor an opportunity to recalculate the QTC date using a more rational method. This may substantially change our view of this finding and may impact importantly on the ultimate labeling.

**APPEARS THIS WAY  
ON ORIGINAL**

cc:

Orig NDA 21-208

HFD-120/DivFile

HFD-120/TLaughren/RKatz/AMosholder/PDavid

**DOC: NDA21208.01**

**APPEARS THIS WAY  
ON ORIGINAL**

**NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST**

NDA <u>21-208</u> <u>3S</u>	
Drug <u>Disintegrating 15 mg, 30 mg, and 45 mg Tablets</u>	Applicant <u>Organon Inc.</u>
RPM <u>Paul David</u>	Phone <u>x4-5530</u>
<input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) Reference listed drug _____	
<input type="checkbox"/> Fast Track	<input type="checkbox"/> Rolling Review Review priority: <input checked="" type="checkbox"/> S <input type="checkbox"/> P
Pivotal IND(s) _____	
Application classifications: Chem Class <u>3</u> Other (e.g., orphan, OTC) _____	PDUFA Goal Dates: Primary <u>10-30-00</u> Secondary <u>12-30-00</u>

Arrange package in the following order:

Indicate N/A (not applicable), X (completed), or add a comment.

**GENERAL INFORMATION:**

- ◆ User Fee Information:     User Fee Paid  
                                    User Fee Waiver (attach waiver notification letter)  
                                    User Fee Exemption
  
- ◆ Action Letter.....  AP  AE  NA
  
- ◆ Labeling & Labels
 

FDA revised labeling and reviews.....	X
Original proposed labeling (package insert, patient package insert) .....	X
Other labeling in class (most recent 3) or class labeling.....	X
Has DDMAC reviewed the labeling? .....	<input type="checkbox"/> Yes (include review) <input checked="" type="checkbox"/> No
Immediate container and carton labels .....	X
Nomenclature review .....	X
  
- ◆ Application Integrity Policy (AIP)  Applicant is on the AIP. This application  is  is not on the AIP.
  
- Exception for review (Center Director's memo)..... \_\_\_\_\_
- OC Clearance for approval..... \_\_\_\_\_

- ◆ Status of advertising (if AP action)  Reviewed (for Subpart H – attach review)  Materials requested in AP letter
- ◆ Post-marketing Commitments N/A
  - Agency request for Phase 4 Commitments.....
  - Copy of Applicant's commitments .....
- ◆ Was Press Office notified of action (for approval action only)?.....  Yes  No
  - Copy of Press Release or Talk Paper.....
- ◆ Patent X
  - Information [505(b)(1)] .....
  - Patent Certification [505(b)(2)].....
  - Copy of notification to patent holder [21 CFR 314.50 (i)(4)].....
- ◆ Exclusivity Summary ..... X
- ◆ Debarment Statement ..... X
- ◆ Financial Disclosure X
  - No disclosable information .....
  - Disclosable information – indicate where review is located .....
- ◆ Correspondence/Memoranda/Faxes ..... X
- ◆ Minutes of Meetings .....
  - Date of EOP2 Meeting \_\_\_\_\_
  - Date of pre NDA Meeting \_\_\_\_\_
  - Date of pre-AP Safety Conference \_\_\_\_\_
- ◆ Advisory Committee Meeting ..... N/A
  - Date of Meeting .....
  - Questions considered by the committee .....
  - Minutes or 48-hour alert or pertinent section of transcript .....
- ◆ Federal Register Notices, DESI documents ..... N/A

**CLINICAL INFORMATION:**

**Indicate N/A (not applicable), X (completed), or add a comment.**

- ◆ Summary memoranda (e.g., Office Director's memo, Division Director's memo, Group Leader's memo) ..... X
- ◆ Clinical review(s) and memoranda ..... X
- ◆ Safety Update review(s) ..... N/A
- ◆ Pediatric Information
  - Waiver/partial waiver (Indicate location of rationale for waiver)  Deferred Pediatric Page.....



NOTE: A new Pediatric Page must be completed at the time of each action even though one was prepared at the time of the last action.

NDA/PLA/PMA # 21-208 Supplement # \_\_\_\_\_ Circle one: SE1 SE2 SE3 SE4 SE5 SE6

HFD-120 Trade and generic names/dosage form: Remeron Softab (mirtazapine) Orally Disintegrating 15 mg, 30 mg, and 45 mg Tablets

Action: AP AE NA

Applicant Organon Therapeutic Class Antidepressant

Indication(s) previously approved N/A

Pediatric information in labeling of approved indication(s) is adequate \_\_\_ inadequate X

Proposed indication in this application Depression

FOR SUPPLEMENTS, ANSWER THE FOLLOWING QUESTIONS IN RELATION TO THE PROPOSED INDICATION.

IS THE DRUG NEEDED IN ANY PEDIATRIC AGE GROUPS? X Yes (Continue with questions) \_\_\_ No (Sign and return the form)

WHAT PEDIATRIC AGE GROUPS IS THE DRUG NEEDED? (Check all that apply)

\_\_\_ Neonates (Birth-1month) \_\_\_ Infants (1month-2yrs) X Children (2-12yrs) X Adolescents(12-16yrs)

- 1. PEDIATRIC LABELING IS ADEQUATE FOR ALL PEDIATRIC AGE GROUPS. Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric age groups. Further information is not required.
- 2. PEDIATRIC LABELING IS ADEQUATE FOR CERTAIN AGE GROUPS. Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for certain pediatric age groups (e.g., infants, children, and adolescents but not neonates). Further information is not required.
- X 3. PEDIATRIC STUDIES ARE NEEDED. There is potential for use in children, and further information is required to permit adequate labeling for this use.
  - a. A new dosing formulation is needed, and applicant has agreed to provide the appropriate formulation.
  - b. A new dosing formulation is needed, however the sponsor is either not willing to provide it or is in negotiations with FDA.
  - X c. The applicant has committed to doing such studies as will be required.
    - X (1) Studies are ongoing,
    - X (2) Protocols were submitted and approved.
    - (3) Protocols were submitted and are under review.
    - (4) If no protocol has been submitted, attach memo describing status of discussions.
  - d. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.
- 4. PEDIATRIC STUDIES ARE NOT NEEDED. The drug/biologic product has little potential for use in pediatric patients. Attach memo explaining why pediatric studies are not needed.
- 5. If none of the above apply, attach an explanation, as necessary.

ARE THERE ANY PEDIATRIC PHASE IV COMMITMENTS IN THE ACTION LETTER? \_\_\_ Yes X No  
ATTACH AN EXPLANATION FOR ANY OF THE FOREGOING ITEMS, AS NECESSARY.

This page was completed based on information from the Remeron, NDA 20-415, NDA files as well as the medical officer's reviews (e.g., medical review, medical officer, team leader).

Signature of Preparer and Title TL, PEP  
cc: Archival NDA #21-208  
HFD-120/Div File  
NDA Action Package

18-22-03  
Date

**CONFIDENTIAL**

**PATENT INFORMATION AND ORIGINAL DECLARATION**

**PATENT INFORMATION**

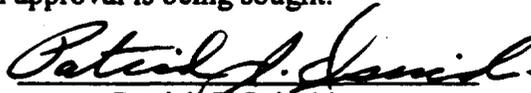
21 CFR §314.53(c)(1)

- (i) U.S. Patent No. 5,178,878  
Expiration Date - January 12, 2010
  
- (ii) Type of Patent - Drug Product (claim 1 to "a solid pharmaceutical dosage form")
  
- (iii) Name of Patent Owner  
  
CIMA Labs, Inc.  
Minneapolis, MN

**ORIGINAL DECLARATION**

21 CFR §314.53(c)(2)

The undersigned declares that Patent No. 5,178,878 covers the formulation, composition and/or method of use of \_\_\_\_\_ This product is the subject of this application for which approval is being sought.



Patrick J. Osinski  
Vice President  
Organon Inc.

0014

**DEBARMENT CERTIFICATION**

Pursuant to Section 306(k)(1) of the Federal Food, Drug and Cosmetic Act, the undersigned certifies that Organon Inc did not and will not use in any capacity the services of any person debarred under subsections (a) or (b) [Section 306(a) or (b)] in connection with the New Drug Application for \_\_\_\_\_, NDA 21-208.



Albert P. Mayo  
Executive Director  
Regulatory Affairs

**APPEARS THIS WAY  
ON ORIGINAL**

**0015**



Organon Inc.

December 14, 1999

Mellon Bank  
Three Mellon Bank Center  
17<sup>th</sup> Floor (FDA 360909)  
Pittsburgh, PA 15259-0001

**Re: Prescription Drug User Fee Act of 1997  
Application Fee Payment for NDA No. 21-208  
Original New Drug Application for Remeron<sup>®</sup> (mirtazapine) Orally Disintegrating  
Tablets  
Organon Inc., 375 Mt. Pleasant Ave., West Orange, NJ 07052**

Dear Sir/Madam:

Pursuant to the above referenced Act, please find enclosed on behalf of Organon Inc., 375 Mt. Pleasant Avenue, West Orange, New Jersey as follows:

Check No \_\_\_\_\_ in the amount of \$136,141.00 related to the Application Fee for \_\_\_\_\_ NDA 21-208. This is an original New Drug Application, which is to be submitted on or about December 30, 1999, for a new dosage form of Remeron<sup>®</sup>(mirtazapine) Tablets.

Should you have any questions, please contact the undersigned at 973-325-4833.

Sincerely,

Albert P. Mayo  
Executive Director  
Regulatory Affairs

Attachment  
Form FDA 3397

Submitted via Federal Express Airbill #810494765379



Organon Inc.  
375 Mt. Pleasant Avenue  
West Orange  
New Jersey 07052  
USA  
Tel.: (973) 325-4500  
Fax: (973)-325-4589

0011

USER FEE COVER SHEET

See Instructions on Reverse Side Before Completing This Form

1. APPLICANT'S NAME AND ADDRESS

Albert P. Mayo  
Organon Inc.  
375 Mt. Pleasant Ave.  
West Orange, NJ 07052

3. PRODUCT NAME

Remeron (mirtazapine) Orally Disintegrating Tablets

4. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?  
IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP  
HERE AND SIGN THIS FORM.

IF RESPONSE IS "YES", CHECK THE APPROPRIATE RESPONSE BELOW:

- THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION.  
 THE REQUIRED CLINICAL DATA ARE SUBMITTED BY  
REFERENCE TO 20-415  
(APPLICATION NO. CONTAINING THE DATA).

2. TELEPHONE NUMBER (include Area Code)

(973) 325-4833

5. USER FEE I.D. NUMBER

3881

6. LICENSE NUMBER / NDA NUMBER

21-208

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

- A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 (Self Explanatory)
- A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE (See Item 7, on reverse side before checking box.)
- THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act (See Item 7, reverse side before checking box.)
- THE APPLICATION IS A PEDIATRIC SUPPLEMENT THAT QUALIFIES FOR THE EXCEPTION UNDER SECTION 736(a)(1)(F) of the Federal Food, Drug, and Cosmetic Act (See Item 7, reverse side before checking box.)
- THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALY (Self Explanatory)

FOR BIOLOGICAL PRODUCTS ONLY

- WHOLE BLOOD OR BLOOD COMPONENT FOR TRANSFUSION
- A CRUDE ALLERGENIC EXTRACT PRODUCT
- AN APPLICATION FOR A BIOLOGICAL PRODUCT FOR FURTHER MANUFACTURING USE ONLY
- AN "IN VITRO" DIAGNOSTIC BIOLOGICAL PRODUCT LICENSED UNDER SECTION 351 OF THE PHS ACT
- BOVINE BLOOD PRODUCT FOR TOPICAL APPLICATION LICENSED BEFORE 9/1/92

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION?

YES  NO

(See reverse side if answered YES)

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment.

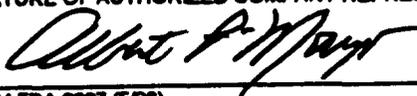
Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

DHHS, Reports Clearance Officer  
Paperwork Reduction Project (0910-0297)  
Hubert H. Humphrey Building, Room 531-H  
200 Independence Avenue, S.W.  
Washington, DC 20201

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

Please DO NOT RETURN this form to this address.

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE



TITLE

Albert P. Mayo  
Executive Director, Regulatory Affairs

DATE

12/14/99

**FINANCIAL DISCLOSURE**

**List of Investigators**

**Study Number**  
22527

**Primary Investigator**  
U.G. Chin-Kon-Sung, M.D.

**Subinvestigators**

---

**APPEARS THIS WAY  
ON ORIGINAL**

### CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

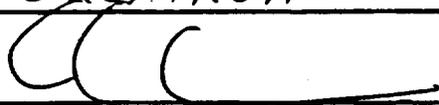
With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

- (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigator	H. G. CHIN - KONSILNIG	
	D. S. KONLKEN	

- (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).
- (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME	TITLE
C. M. GREENHOLT	DIR CLIN. TRIALS OPERATIONS
FIRM/ORGANIZATION	
N. U. ORGANON	
SIGNATURE	DATE
	15 Dec 1999

#### Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right.

Department of Health and Human Services  
Food and Drug Administration  
5600 Fishers Lane, Room 14C-03  
Rockville, MD 20857

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
Public Health Service  
Food and Drug Administration

Form Approved: OMB No. 0910-0206  
Expiration Date: 3/31/02

### CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkboxes.

(1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in the product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigator	R. WEIDGAAE	
	A.J. HEUKELS	
	E.P.H. COLBERS	

(2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

(3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME C.M. GROENHOUT	TITLE DIR. CLINICAL TRIAL OPERATIONS
FIRM/ORGANIZATION N.V. ORGANON	
SIGNATURE 	DATE 23 Dec 1999

#### Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address on the right.

Department of Health and Human Services  
Food and Drug Administration  
5600 Fishers Lane, Room 14C-03  
Rockville, MD 20857

**Number of Pages**  
**Redacted** 55



Draft Labeling  
(not releasable)

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: March 15, 2000

TO: Associate Director  
International Operations Drug Group  
Division of Emergency and Investigational Operations  
(HFC-130)

FROM: David A. Lepay, M.D., Ph.D. 151 2/16/2000  
Director  
Division of Scientific Investigations (HFD-45)

THROUGH: C.T. Viswanathan, Ph.D. CTV 3/15/00  
Associate Director (Bioequivalence)  
Division of Scientific Investigations (HFD-48)

SUBJECT: FY 2000 High Priority CDER User Fee NDA, Pre-approval  
Data Validation Inspection, Bioresearch Monitoring,  
Human Drugs, CP 7348.001

RE: NDA 21-208  
DRUG: \_\_\_\_\_ (Mitrzapine) Orally Disintegrating  
15, 30 and 45 mg Tablets  
SPONSOR: Organon, Inc.  
West Orange, NJ

This memo requests that you arrange for an inspection of the clinical and analytical portions of the following bioequivalence study.

Protocol: #22527: A Single-Dose, Fasting, Open, 2-way  
Crossover Bioequivalence Trial on Org 3770 30 mg  
Orally Disintegrating Tablet / \_\_\_\_\_ Versus 30  
mg Org 3770 Marketed Tablet in 40 Healthy  
Volunteers.

Clinical Site: Farma Research BV  
St. Hubertusstraat 2  
6531 LB Nijmegen  
The Netherlands  
TEL: 011 31 24 3831844

Clinical Investigator: U.G. Chin-Kon-Sung, M.D.

**Sponsor Contact:** Albert Mayo, Executive Director, Regul. Affairs  
TEL: (973) 325-4500

Please check the batch numbers of both the test and the reference drug formulations used in the studies with the descriptions in documents submitted to the Agency. If study formulations have not been submitted to the Agency previously, samples of both the test and reference drug formulations should be collected and mailed to the Division of Drug Analysis, St. Louis, MO, for screening.

Please have the records of all study subjects audited. The subject records in the ANDA submission should be compared to the original documents at the firm. In addition to the standard investigation involving the source documents, case report forms, adverse events, concomitant medications, number of evaluable subjects, drug accountability, etc., the files of communication between the clinical site and the sponsor should be examined for their content.

**Analytical Site:**

\_\_\_\_\_

TE \_\_\_\_\_

**Document:** Experiment #MT022 (Internal Archive #349)

**Title:** Bioanalysis of Org 3770 in Human Plasma Samples  
from Clinical Trial 22527

**Analytical  
Investigator:**

\_\_\_\_\_

**Instrumentation:** GC with Nitrogen-Phosphorous Detection

All pertinent items related to the analytical method should be examined and the sponsor's data should be audited. The chromatograms in the ANDA submission should be compared with the original documents at the firm. The method validation and the actual assay of plasma samples, as well as the variability between and within runs, Q.C., stability, the number of repeat assays of subject plasma samples, and the reason for such repetitions, if any, should be examined. The SOPs for the various procedures need to be scrutinized. In addition to the standard investigation involving source documents, the files of communication between the analytical site and the sponsor should be examined for their content.

Following identification of the investigator, background material will be forwarded directly. A member of the Bioequivalence Team from the Division of Scientific Investigations Staff will participate in the inspections.

Due to user fee deadlines, the inspection must be completed by July 15, 2000.

Headquarters Contact Person: Sriram Subramaniam, Ph.D.  
(301) 827-5455

CC:

HFA-224

HFD-45/Lepay

HFD-48/Fujiwara/Subramaniam(2)/CF

HFD-120/Katz/David

HFD-860/Baweja/Zhou

Draft: SS 2/23/00

Edit: MKY

DSI:5321; O:\BE\assigns\bio21208.doc

APPEARS THIS WAY  
ON ORIGINAL

MEMORANDUM

Date: 3/3/00

To: HFD-340/Division of Scientific Investigations

Through: Russell Katz, M.D., Director, Review Division/HFD-120

From: Paul David, Review Division PM/HFD-120

Subject: Request for Clinical Inspections  
 NDA 21-208  
 Sponsor Name: Organon  
 Drug Trade Name and Generic Name: \_\_\_\_\_ (mirtazapine) Orally  
 Disintegrating 15 mg, 30 mg, and 45 mg Tablets

ISI, 3/3/00

ISI

Section A: Protocol/Site Identification

As discussed with you, the following protocols/sites essential for approval have been identified for inspection. These sites are listed in order of priority. We have previously sent DSI the study report.

<u>Indication</u>	<u>Protocol #</u>	<u>Site (Name and Address)</u>
Depression	Study 22527	Netherlands

International inspection requests (Section B) or requests for five or more inspections (Section C) require sign-off by the ORM Division Director and forwarding through the Director, DSI.

Section B (optional): International Inspections

We have requested inspections because (please check appropriate statements):

- There are insufficient domestic data; or
- Only foreign data are submitted to support an application; or
- Domestic and foreign data show conflicting results pertinent to decision-making; or
- There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, significant human subject protection violations.
- Other \_\_\_\_\_

Section D: Goal Date for Completion

We request that the inspections be performed and the Inspection Summary Results be provided by (inspection summary goal date) August 2000. We intend to issue an action letter on this application by (action goal date) 10-20-00

Should you require any additional information, please contact Paul David; 594-5530

Distribution: IND/NDA21-208  
 HFD-120/Division File  
 HFD-120/PDavid  
 HFD-4#/GCPB Reviewer  
 HFD-45/Program Management Staff



made Organon aware of the regulation and had previously requested sufficient medication for administration, reserve, and excess. Because the sponsor is not an independent third party, this violation of 21CFR320.38(h) and the 4/28/93 Final Rule prevents assurance that there was no false substitution. In addition, the 10 tablet quantity would have been insufficient for repeat testing.

Following the inspection at \_\_\_\_\_ (7/7-7/00), Form 483 was issued, listing the following objectionable finding:

1. Run #MT022k, Period 1 (for subjects 19, 20, and 21) was accepted although two of three "low" QC results failed the acceptance criterion ( $\pm 20\%$ ). The run acceptance criterion specified by SOP #73G16-01 was that two of three QCs at each concentration should pass.

The low QC failure was apparently due to a chromatographic interference appearing late in the run. We note that comparable SOPs at most other sites would have allowed acceptance of this run, since 6 of 9 QCs passed.

Conclusion:

Due to the failure to meet the requirement to retain the study drug samples, we cannot assure the identity of the dosage forms used in this bioequivalence study. We recommend that the results of this study be not used in your review.

After you have reviewed this memo, please append it to the original NDA submission.

*Michael F. Skelly*  
Michael F. Skelly, Ph.D.

**APPEARS THIS WAY  
ON ORIGINAL**

Final Classifications:

Farma Research

- VAI

- VAI

CC:

HFA-224

HFC-130/Kadar

HFD-45/rf

HFD-48/Fujiwara/Skelly/cf

HFD-120/David

HFD-860/Baweja/Zhou

HFR-SW350/Kuchenthal

File:5321; O:\BE\21208org.mit.doc

**APPEARS THIS WAY  
ON ORIGINAL**

NOV 0 4 1999

**CONSULTATION RESPONSE**  
**Office of Post-Marketing Drug Risk Assessment**  
**(OPDRA; HFD-400)**

**DATE SENT:** October 29, 1999

**DUE DATE:** N/A

**OPDRA CONSULT #:** 99-042

**TO (Divisions):**

Russ Katz, MD  
Director, Division of Neuropharmacological Drug Products  
HFD-120

**PRODUCT NAME:**

(Mirtazapine Tablets)

**IND #:**

**MANUFACTURER:** Organon

**CASE REPORT NUMBER(S):** Not applicable.

**SUMMARY:**

In response to a consult from the Division of Neuropharmacological Drug Products, OPDRA conducted a review of the proposed proprietary name " " to determine the potential for confusion with approved proprietary and generic names as well as pending names.

**OPDRA RECOMMENDATION:**

OPDRA has no objections to the use of the proprietary name " "

*JS*  
\_\_\_\_\_  
Jerry Phillips  
Associate Director for Medication Error Prevention  
Office of Post-Marketing Drug Risk Assessment  
Phone: (301) 827-3246  
Fax: (301) 827-5189

*PS*  
\_\_\_\_\_  
Peter Honig, MD  
Deputy Director  
Office of Post-Marketing Drug-Risk Assessment  
Center for Drug Evaluation and Research  
Food and Drug Administration

Office of Post-Marketing Drug Risk Assessment  
HFD-400; Rm 15B03  
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: October 12, 1999  
IND# 20-522  
NAME OF DRUG: \_\_\_\_\_ (Mirtazapine Tablets)  
IND HOLDER: Organon

I. INTRODUCTION:

This consult is in response to a request sent on September 9, 1999, from the Division of Neuropharmacological Drug Products (HFD-120) to review the proposed proprietary drug name, \_\_\_\_\_ regarding potential name confusion with existing proprietary/generic drug names.

The proposed name was also submitted to CDER's Labeling and Nomenclature Committee (LNC) on July 26, 1999. The committee reviewed the name on September 24, 1999 and determined it was unacceptable. The committee commented ' \_\_\_\_\_

PRODUCT INFORMATION

\_\_\_\_\_ manufactured by Organon, was submitted under \_\_\_\_\_. Draft container labels, carton and insert labeling were not available for review. According to the project manager, \_\_\_\_\_ is a rapidly dissolving formulation of mirtazapine. The dosing and frequency of this formulation will be identical to the marketed immediate release tablets (Remeron). \_\_\_\_\_ will be indicated for the treatment of depression. The recommended starting dose for mirtazapine is 15 mg/day increasing up to 45 mg/day and the mechanism of action is unknown.

II. RISK ASSESSMENT:

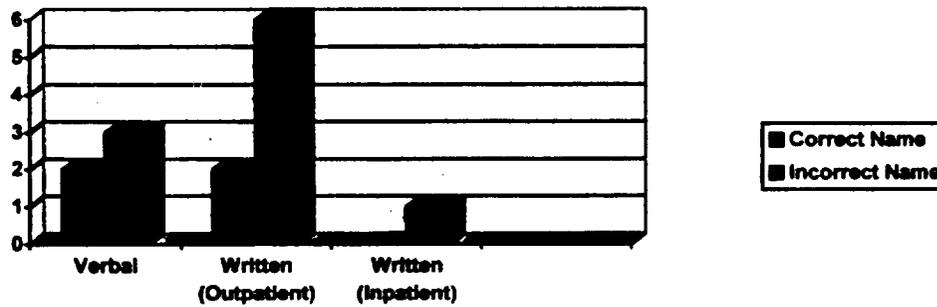
In order to predict the potential for medication errors and to determine the degree of confusion associated with the proposed name, ' \_\_\_\_\_ ', with other approved and unapproved drug names, the medication error staff of OPDRA searched the American Drug Index (43rd Edition), Physicians' Desk Reference [53 Edition; 1999], Drug Facts and Comparisons (Updated Monthly) and the Electronic Orange Book for potential sound-alike or look-alike names to approved drugs. OPDRA also searched the Agency's internal databases, Establishment Evaluation System (EES), Drug Product Reference File (DPR), and the LNC database for potential sound-alike or look-alike names to unapproved/approved drugs. In addition, OPDRA conducted an internal study of written and verbal analysis of the proposed proprietary name requesting health care practitioners within OPDRA to evaluate potential errors in handwriting and verbal communication of the name. This exercise was conducted to simulate an actual practice setting.

Methodology:

This study involved 19 health professionals comprised of pharmacists, physicians, and nurses within OPDRA to determine the degree of confusion of ' \_\_\_\_\_ ' with other drug names due to the similarity in handwriting and verbal pronunciation of the name. OPDRA staff members wrote one inpatient and one outpatient order, each consisting of two known drug products and a prescription for \_\_\_\_\_ . These prescriptions were scanned into the computer and a random sample of the written orders, were then delivered to the participating health professionals via e-mail. In addition, two pharmacists recorded three outpatient prescriptions, two known drugs and a prescription for \_\_\_\_\_ . The voice mail messages were then sent to the participating health professionals for their review. After receiving either the written or verbal prescription orders, the participants sent their interpretations of the orders vial e-mail to the medication error staff. After receiving the interpretations, the correct spelling of the proposed proprietary name was sent to the health professionals with a request for handwriting samples of the names. The medication error staff then reviewed the samples of the handwritten names.

Results:

We received responses from fourteen participants, four of which interpreted the correct name. Eight participants interpreted outpatient prescription orders, five interpreted verbal orders and one interpreted an inpatient order. The results are as follows:



29% responded with the correct name " \_\_\_\_\_ " 71% responded with the correct modifier \_\_\_\_\_ . However, the remainder of participants responded with an incorrect proprietary name, incorrect modifier or no modifier at all.

## FOCUS GROUP FINDINGS

The group discussion focused on the modifier "easy" since "Remeron" is an approved proprietary name marketed by Organon under NDA 20-415 (Remeron Tablets 15 mg, 30 mg and 45 mg). "easy" is a common medical abbreviation for "easy" (vaccine)" and we did not consider this to be a potential problem. The group also discussed the connotation of "easy" associated with the modifier "easy". The focus group considered the use of "easy" in conjunction with the proprietary name "Remeron" fanciful as defined in 21 CFR 201.10(c)(3) in that it implies the product has some unique effectiveness or composition. Therefore, we consulted the Division of Drug Marketing, Advertising, and Communication (DDMAC) via telephone for their review and comment. DDMAC considered the name misleading, in that it implied a broader indication. In addition, DDMAC commented "easy" has such a broad connotation and could even be interpreted as a quality of life claim.

## DISCUSSION:

The results of the internal study did not uncover any names that might have the potential to be confused with approved or pending drug products nor did any of the searches in available texts, databases or handwriting samples. However, the majority of participants did not evaluate "Remeron" correctly. We recognize that low scores of correct interpretations would be common for all unapproved drug product names because health professionals are not familiar with the name. However, in this case "Remeron" has been marketed since June 14, 1996 and we expected a greater number of correct responses.

An AERS search was conducted to identify problems associated with name confusion post-marketing with "Remeron". The search revealed only one case of confusion between Remeron and Zoloft. Remeron is marketed as 15 mg, 30 mg and 45 mg tablets and Remeron will be marketed a similar fashion. Zoloft is marketed as 25 mg, 50 mg and 100 mg tablets. There are no overlapping strengths involved. OPDRA concluded this case was most likely an isolated incidence.

OPDRA recognizes the potential for confusion between Remeron and Remeron. The use of a modifier in conjunction Remeron will aid in product differentiation. The Agency has approved some orally disintegrating tablet formulations (MAXALT-MLT and Claritin Reditabs), in which both products have modifiers to distinguish themselves from their immediate release formulations. Remeron and Remeron will still have overlapping strengths, similar names, and most likely similar labeling from the same manufacturer. Therefore, it will be extremely important to differentiate their strengths and labeling, in addition to the name, to prevent medication errors due to confusion between the two products. Please note that in a previous OPDRA consult (99-009), dated May 25, 1999, numerous reports of confusion were received about the net quantity and strength being confused. It will be important that the firm follow similar labeling, as outlined in your June 30, 1999 letter to the firm.

**APPEARS THIS WAY  
ON ORIGINAL**



DIVISION of Neuropharmacological Drug Products  
HFD-120, Room 4030  
1451 Rockville Pike  
Rockville, MD 20852

F. David



TO:		FROM:	
Name:	<b>Carol Schickman, Regulatory Affairs</b>	Name:	<b>Paul David, Regulatory Project Manager</b>
Fax No:	973-325-4769	Fax No:	(301) 594-2858
Phone No:	973-325-4655	Phone No:	(301) 594-2850
Location:	Organon	Location:	FDA, Division of Neuropharmacological Drug Products

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Comments:

Carol,  
OPDRA has completed its review of your proposed tradename of Remeron \_\_\_\_\_ submitted to the mirtazapine orally disintegrating tablets NDA, 21-208, in an amendment dated 4-11-00, and they found the name unacceptable for the following reasons:

1. \_\_\_\_\_
2. \_\_\_\_\_

Therefore, please submit another proposed tradename to NDA 21-208 for evaluation.

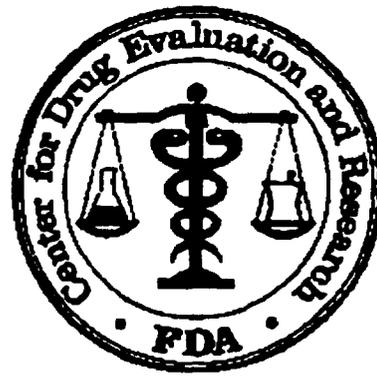
Thank you,  
Paul David

NDA 21-208  
HFD-120/Div. File  
HFD-120/R.Katz/T.Laughren/A.Mosholder  
HFD-120/P.David  
HFD-120/

- 151  
c/c 26 cas

**APPEARS THIS WAY  
ON ORIGINAL**

HFD-120, Room 4030  
1451 Rockville Pike  
Rockville, MD 20852



TO:		FROM:	
Name:	<b>Carol Shichman, Regulatory Affairs</b>	Name:	<b>Paul David, Regulatory Project Manager</b>
Fax No:	<b>973-325-4769</b>	Fax No:	<b>(301) 594-2858</b>
Phone No:	<b>973-325-4655</b>	Phone No:	<b>(301) 594-2850</b>
Location:	<b>Organon</b>	Location:	<b>FDA, Division of Neuropharmacological Drug Products</b>

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Comments:

Carol,

We have completed a review of the proposed tradenames submitted on 6-19-00, to the Mirtazapine Orally Disintegrating application, NDA 21-208, and we have found the names to be unacceptable. Your correspondence requested an expedited review of the following tradenames: \_\_\_\_\_ (mirtazapine) Orally Disintegrating Tablets and \_\_\_\_\_ (mirtazapine) Orally Disintegrating Tablets.

The Agency's expert panel discussed this proposal and have found the names unacceptable for the following reasons:

1. The \_\_\_\_\_ modifier could be easily confused and interpreted as \_\_\_\_\_ and the patient could receive 5 tablets instead of 1.
2. The \_\_\_\_\_ modifier could also be confused as \_\_\_\_\_ and interpreted as 5 tablets.

We note that the Agency's expert panel has already found one of your proposed tradenames, Remeron Soltab (mirtazapine) Orally Disintegrating Tablets, acceptable. You may choose to use this tradename or submit another alternative tradename.

If you have any questions, please feel free to contact me directly.  
Paul David