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NDA 20415

1 OF 8

NDA 20415

NDA 20-415

JUN 14 1996

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

Dear Mr. Mayo:

Please refer to your New Drug Application (and your resubmission dated January 26, and received on January 30, 1995) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Remeron™ (mirtazapine) 15 and 30 mg Tablets to treat depression.

We also refer to an Agency approvable letter dated January 26, 1996, and we also acknowledge receipt of your additional communications dated March 15, and May 10, 1996, providing for responses to our approvable letter.

We have completed our 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 draft labeling dated May 10, 1996. Accordingly, the application is approved effective as of the date of this letter.

Accompanying this letter (ATTACHMENT) is the labeling, including the revisions agreed to, that should be used for marketing this drug product. These revisions are terms of the NDA approval. Marketing the product before making the agreed upon revisions in the product's labeling may render the product misbranded and an unapproved new drug.

We have the following additional comments:

Phase 4 Commitments

We remind you of your Phase 4 commitments agreed upon in your submissions dated March 15, and May 10, 1996. These commitments are listed below. Protocols, data, and final reports should be submitted to your IND for this product and a copy of the cover letter sent to this NDA. Should an IND not be required to meet your Phase 4 commitments, please submit protocols, data, and final reports to this NDA as correspondence. For administrative purposes, all submissions, including labeling supplements, relating to these Phase 4 commitments must be clearly designated "Phase 4 Commitments".

1. Exploration of Dose Response for Effectiveness/Exploration of Dose Response and Time Course for Sedative Effects of Mirtazapine

We note your commitment in correspondence dated May 10, 1996, to conduct a fixed dose response/somnolence study that will explore dose response for both antidepressant effectiveness and for somnolence. We also note your commitment to initiate this study in early 1997 and to complete this study by mid 1998.

2. Long-Term Efficacy Studies

We note your commitment in correspondence dated May 10, 1996, to conduct a relapse prevention study. We also note your commitment to initiate this study in early 1997 and to complete this study by early 1999.

3. Mouse Carcinogenicity Study

We accept your plan to perform a pilot 2 week dietary study in mice. Depending on the results of this study, we acknowledge your commitment to conduct a 3 month dietary administration study in mice to obtain exposure data which will allow us to determine whether or not the mouse carcinogenicity study was adequate.

Biopharmaceutics

We note your agreement to the following dissolution method and specification for all tablet strengths:

Apparatus:
Paddle Speed:
Medium:
Specification:

Manufacturing and Controls

As acknowledged in your correspondence dated May 10, 1996, the Agency is approving an initial 24-month expiration dating period based upon your currently available 24 -month data.

Special Reporting Requirement for Selected Spontaneous Reports

In order to facilitate our efficient review and evaluation of data pertinent to hematologic and hepatic toxicity, we ask that you submit any spontaneous reports for adverse events of these types as 15 day reports.

Please submit sixteen 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 "FINAL PRINTED LABELING" for

Should additional information relating to the safety and effectiveness of the drug become available, revision of that labeling may be required.

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 concerning this NDA, please contact Mr. Paul David, Project Manager, at (301) 594-2777.

Sincerely yours,

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

ATTACHMENT

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REMERON™ (mirtazapine) Tablets

DESCRIPTION

REMERON™ (mirtazapine) is an antidepressant for oral administration. It has a tetracyclic chemical structure, unrelated to selective serotonin reuptake inhibitors, tricyclics or monoamine oxidase inhibitors (MAOI). Mirtazapine belongs to the piperazino-azepine group of compounds. It is designated 1,2,3,4,10,14b-hexahydro-2-methylpyrazino [2,1-a] pyrido [2,3-c] benzazepine and has the empirical formula of $C_{17}H_{19}N_3$. Its molecular weight is 265.36. The structural formula is the following and it is the racemic mixture:

[Insert structural formula here.]

Mirtazapine is a white to creamy white crystalline powder which is slightly soluble in water.

REMERON™ is supplied for oral administration as scored film-coated tablets containing 15 or 30 mg of mirtazapine. Each tablet also contains corn starch, hydroxypropyl cellulose, magnesium stearate, colloidal silicon dioxide, lactose and other inactive ingredients.

CLINICAL PHARMACOLOGY

Pharmacodynamics

The mechanism of action of REMERON™ (mirtazapine), as with other antidepressants, is unknown.

Evidence gathered in preclinical studies suggests that mirtazapine enhances central noradrenergic and serotonergic activity. These studies have shown that mirtazapine acts as an antagonist at central presynaptic α_2 adrenergic inhibitory

autoreceptors and heteroreceptors, an action that is postulated to result in an increase in central noradrenergic and serotonergic activity.

Mirtazapine is a potent antagonist of 5-HT₂ and 5-HT₁ receptors. Mirtazapine has no significant affinity for the 5-HT_{1A} and 5-HT_{1B} receptors.

Mirtazapine is a potent antagonist of histamine (H₁) receptors, a property that may explain its prominent sedative effects.

Mirtazapine is a moderate peripheral α_1 adrenergic antagonist, a property that may explain the occasional orthostatic hypotension reported in association with its use.

Mirtazapine is a moderate antagonist at muscarinic receptors, a property that may explain the relatively low incidence of anticholinergic side effects associated with its use.

Pharmacokinetics

REMERON[®] (mirtazapine) is rapidly and completely absorbed following oral administration and has a half-life of about 20-40 hours. Peak plasma concentrations are reached within about 2 hours following an oral dose. The presence of food in the stomach has a minimal effect on both the rate and extent of absorption and does not require a dosage adjustment.

Mirtazapine is extensively metabolized after oral administration. Major pathways of biotransformation are demethylation and hydroxylation followed by glucuronide conjugation. In-vitro data from human liver microsomes indicate that cytochrome 2D6 and 1A2 are involved in the formation of the 8-hydroxy metabolite of mirtazapine, whereas cytochrome 3A is considered to be responsible for the formation of the N-desmethyl and N-oxide metabolite. Mirtazapine has an absolute bioavailability of about 50%. It is eliminated predominantly via urine (75%) with 15% in feces. Several unconjugated metabolites possess pharmacological activity but are present in the plasma at very low levels. The (-) enantiomer has an elimination half-life that is approximately twice as long as the (+) enantiomer and therefore achieves plasma levels that are about three times as high as that of the (+) enantiomer.

Plasma levels are linearly related to dose over a dose range of 15 to 80 mg. The mean elimination half-life of mirtazapine

after oral administration ranges from approximately 20-40 hours across age and gender subgroups, with females of all ages exhibiting significantly longer elimination half-lives than males (mean half-life of 37 hours for females vs 26 hours for males). Steady state plasma levels of mirtazapine are attained within 5 days, with about 50% accumulation (accumulation ratio = 1.5).

Mirtazapine is approximately 85% bound to plasma proteins over a concentration range of 0.01 to 10 µg/mL.

Population Subgroups

Liver Disease - Following a single 15 mg oral dose of mirtazapine, the oral clearance of mirtazapine was decreased by approximately 30% in hepatically impaired patients compared to subjects with normal hepatic function. Caution is indicated in administering REMERON[™] to patients with compromised hepatic function (see Precautions and Dosage and Administration).

Renal Disease - Following a single 15 mg oral dose of mirtazapine, patients with moderate [glomerular filtration rate (GFR) = 11-39 mL/min/1.73 m²] and severe [GFR < 10 mL/min/1.73 m²] renal impairment had reductions in mean oral clearance of mirtazapine of about 30% and 50%, respectively, compared to normal subjects. Caution is indicated in administering REMERON[™] to patients with compromised renal function (see Precautions and Dosage and Administration).

Elderly Patients - Following oral administration of mirtazapine 20 mg/day for 7 days to subjects of varying ages (range, 25-74), oral clearance of mirtazapine was reduced in the elderly compared to the younger subjects. The differences were most striking in males, with a 40% lower clearance in elderly males compared to younger males, while the clearance in elderly females was only 10% lower compared to younger females. Caution is indicated in administering REMERON[™] to elderly patients (see Precautions and Dosage and Administration).

Clinical Trials Showing Effectiveness

The efficacy of REMERON[™] (mirtazapine) as a treatment for depression was established in four placebo-controlled, 6-week trials in adult outpatients meeting DSM-III criteria for major depression. Patients were titrated with mirtazapine from a dose range of 5 mg up to 35 mg/day. Overall, these studies

demonstrated mirtazapine to be superior to placebo on at least three of the following four measures: 21-Item Hamilton Depression Rating Scale (HDRS) total score; HDRS Depressed Mood Item; CGI Severity score; and Montgomery and Asberg Depression Rating Scale (MADRS). Superiority of mirtazapine over placebo was also found for certain factors of the HDRS including anxiety/somatization factor and sleep disturbance factor. The mean mirtazapine dose for patients who completed these four studies ranged from 21 to 32 mg/day. A fifth study of similar design utilized a higher dose (up to 50 mg) per day and also showed effectiveness.

Examination of age and gender subsets of the population did not reveal any differential responsiveness on the basis of these subgroupings.

INDICATIONS AND USAGE

REMERON[®] (mirtazapine) Tablets are indicated for the treatment of depression.

The efficacy of REMERON[®] in the treatment of depression was established in six week controlled trials of outpatients whose diagnoses corresponded most closely to the Diagnostic and Statistical Manual of Mental Disorders - 3rd edition (DSM-III) category of major depressive disorder (see CLINICAL PHARMACOLOGY).

A major depressive episode (DSM-IV) implies a prominent and relatively persistent (nearly every day for at least 2 weeks) depressed or dysphoric mood that usually interferes with daily functioning, and includes at least five of the following nine symptoms: depressed mood, loss of interest in usual activities, significant change in weight and/or appetite, insomnia or hypersomnia, psychomotor agitation or retardation, increased fatigue, feelings of guilt or worthlessness, slowed thinking or impaired concentration, a suicide attempt or suicidal ideation.

The antidepressant effectiveness of REMERON[®] (mirtazapine) in hospitalized depressed patients has not been adequately studied.

The effectiveness of REMERON[®] in long-term use, that is, for more than 6 weeks, has not been systematically evaluated in controlled trials. Therefore, the physician who elects to use REMERON[®] for extended periods should periodically evaluate the

long-term usefulness of the drug for the individual patient.

CONTRAINDICATIONS

REMERON™ (mirtazapine) Tablets are contraindicated in patients with a known hypersensitivity to mirtazapine.

WARNINGS

Agranulocytosis

In premarketing clinical trials, two (one with Sjögren's Syndrome) out of 2,796 patients treated with REMERON™ (mirtazapine) Tablets developed agranulocytosis [absolute neutrophil count (ANC) < 500/mm³ with associated signs and symptoms, e.g., fever, infection, etc.] and a third patient developed severe neutropenia [ANC < 500/mm³ without any associated symptoms]. For these three patients, onset of severe neutropenia was detected on days 61, 9, and 14 of treatment, respectively. All three patients recovered after Remeron was stopped. These three cases yield a crude incidence of severe neutropenia (with or without associated infection) of approximately 1.1 per thousand patients exposed, with a very wide 95% confidence interval, i.e., 2.2 cases per 10,000 to 3.1 cases per 1000. If a patient develops a sore throat, fever, stomatitis or other signs of infection, along with a low WBC count, treatment with REMERON™ should be discontinued and the patient should be closely monitored.

MAO Inhibitors

In patients receiving other antidepressants in combination with a monoamine oxidase inhibitor (MAOI) and in patients who have recently discontinued an antidepressant drug and then are started on an MAOI, there have been reports of serious, and sometimes fatal, reactions, e.g., including nausea, vomiting, flushing, dizziness, tremor, myoclonus, rigidity, diaphoresis, hyperthermia, autonomic instability with rapid fluctuations of vital signs, seizures, and mental status changes ranging from agitation to coma. Although there are no human data pertinent to such an interaction with REMERON™, it is recommended that REMERON™ not be used in combination with an MAOI, or within 14 days of initiating or discontinuing therapy with an MAOI.

PRECAUTIONS

General

Somnolence

In U.S. controlled studies, somnolence was reported in 54% of patients treated with REMERON[™] (mirtazapine), compared to 18% for placebo and 60% for amitriptyline. In these studies, somnolence resulted in discontinuation for 10.4% of Remeron treated patients, compared to 2.2% for placebo. It is unclear whether or not tolerance develops to the somnolent effects of Remeron. Because of Remeron's potentially significant effects on impairment of performance, patients should be cautioned about engaging in activities requiring alertness until they have been able to assess the drug's effect on their own psychomotor performance (see Information for Patients).

Dizziness

In U.S. controlled studies, dizziness was reported in 7% of patients treated with REMERON[™] (mirtazapine), compared to 3% for placebo and 14% for amitriptyline. It is unclear whether or not tolerance develops to the dizziness observed in association with the use of Remeron.

Increased Appetite/Weight Gain

In US controlled studies, appetite increase was reported in 17% of patients treated with REMERON[™] (mirtazapine), compared to 2% for placebo and 6% for amitriptyline. In these same trials, weight gain of $\geq 7\%$ of body weight was reported in 7.5% of patients treated with mirtazapine, compared to 0% for placebo and 5.9% for amitriptyline. In a pool of premarketing US studies, including many patients in long-term, open label treatment, 8% of patients receiving Remeron discontinued for weight gain.

Cholesterol/Triglycerides

In U.S. controlled studies, nonfasting cholesterol increases to $\geq 20\%$ above the upper limits of normal were observed in 15% of patients treated with REMERON[™] (mirtazapine), compared to 7% for placebo and 8% for amitriptyline. In these same studies, nonfasting triglyceride increases to ≥ 500 mg/dL were observed in 6% of patients treated with mirtazapine, compared to 3% for placebo and 3% for amitriptyline.

Activation of Mania/Hypomania

Mania/hypomania occurred in approximately 0.2% (3/1,299 patients) of REMERON[™] (mirtazapine) treated patients in U.S. studies. Although the incidence of mania/hypomania was very low during treatment with mirtazapine, it should be used carefully in patients with a history of mania/hypomania.

Seizures

In pre-marketing clinical trials only one seizure was reported among the 2,796 U.S. and non-U.S. patients treated with REMERON[™] (mirtazapine). However, no controlled studies have been carried out in patients with a history of seizures. Therefore, care should be exercised when mirtazapine is used in these patients.

Suicide

Suicidal ideation is inherent in depression and may persist until significant remission occurs. As with any patient receiving antidepressants, high-risk patients should be closely supervised during initial drug therapy. Prescriptions of REMERON[™] (mirtazapine) should be written for the smallest quantity consistent with good patient management, in order to reduce the risk of overdose.

Use in patients with concomitant illness

Clinical experience with REMERON[™] (mirtazapine) 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.

Mirtazapine 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. Mirtazapine was not associated with clinically significant ECG abnormalities in U.S. and non-U.S. placebo controlled trials. Mirtazapine 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[™] 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).

Mirtazapine clearance is decreased in patients with moderate [glomerular filtration rate (GFR) = 11-39 mL/min/1.73 m²] and severe [GFR < 10 mL/min/1.73 m²] renal impairment, and also in patients with hepatic impairment (See Pharmacokinetic Subsection of CLINICAL PHARMACOLOGY). Caution is indicated in administering REMERON[™] to such patients (see DOSAGE AND ADMINISTRATION).

Information for patients

Physicians are advised to discuss the following issues with patients for whom they prescribe REMERON[™]:

Agranulocytosis

Patients who are to receive REMERON[™] (mirtazapine) should be warned about the risk of developing agranulocytosis. Patients should be advised to contact their physician if they experience any indication of infection such as fever, chills, sore throat, mucous membrane ulceration or other possible signs of infection. Particular attention should be paid to any flu-like complaints or other symptoms that might suggest infection.

Interference with Cognitive and Motor Performance

REMERON[™] (mirtazapine) may impair judgement, thinking, and, particularly, motor skills, because of its prominent sedative effect. The drowsiness associated with mirtazapine use may

impair a patient's ability to drive, use machines or perform tasks that require alertness. Thus, patients should be cautioned about engaging in hazardous activities until they are reasonably certain that Remeron therapy does not adversely affect their ability to engage in such activities.

Completing Course of Therapy

While patients may notice improvement with REMERON[™] (mirtazapine) therapy in 1 to 4 weeks, they should be advised to continue therapy as directed.

Concomitant medication

Patients should be advised to inform their physician if they are taking, or intend to take, any prescription or over-the-counter drugs since there is a potential for REMERON[™] (mirtazapine) to interact with other drugs.

Alcohol

The impairment of cognitive and motor skills produced by REMERON[™] (mirtazapine) has been shown to be additive with those produced by alcohol. Accordingly, patients should be advised to avoid alcohol while taking mirtazapine.

Pregnancy

Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during REMERON[™] (mirtazapine) therapy.

Nursing

Patients should be advised to notify their physician if they are breast-feeding an infant.

Laboratory tests

There are no routine laboratory tests recommended.

Drug Interactions

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).

Drugs Affecting Hepatic Metabolism

The metabolism and pharmacokinetics of REMERON[™] (mirtazapine) may be affected by the induction or inhibition of drug-metabolizing enzymes.

Drugs that are Metabolized by and/or Inhibit Cytochrome P450 Enzymes

Many drugs are metabolized by and/or inhibit various cytochrome P450 enzymes, e.g., 2D6, 1A2, 3A4, etc. In vitro studies have shown that REMERON[™] (mirtazapine) is a substrate for several of these enzymes, including 2D6, 1A2, and 3A4. While in vitro studies have shown that mirtazapine is not a potent inhibitor of any of these enzymes, an indication that mirtazapine is not likely to have a clinically significant inhibitory effect on the metabolism of other drugs that are substrates for these cytochrome P450 enzymes, the concomitant use of mirtazapine with most other drugs metabolized by these enzymes has not been formally studied. Consequently, it is not possible to make any definitive statements about the risks of coadministration of mirtazapine with such drugs.

Alcohol

Concomitant administration of alcohol (equivalent to 60 g) had a minimal effect on plasma levels of REMERON[™] (15 mg) in 6 healthy male subjects. However, the impairment of cognitive and motor skills produced by REMERON[™] were shown to be additive with those produced by alcohol. Accordingly, patients should be advised to avoid alcohol while taking REMERON[™].

Diazepam

Concomitant administration of diazepam (15 mg) had a minimal effect on plasma levels of mirtazapine (15 mg) in 12 healthy subjects. However, the impairment of motor skills produced by REMERON[™] has been shown to be additive with those caused by diazepam. Accordingly, patients should be advised to avoid diazepam and other similar drugs while taking REMERON[™].

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Carcinogenicity studies were conducted with REMERON[™] (mirtazapine) given in the diet at doses of 2, 20, and 200

mg/kg/day to mice and 2, 20, and 60 mg/kg/day to rats. The highest doses used are approximately 20 and 12 times the maximum recommended human dose (MRHD) of 45 mg/day on a mg/m² basis in mice and rats, respectively. There was an increased incidence of hepatocellular adenoma and carcinoma in male mice at the high dose. In rats, there was an increase in hepatocellular adenoma in females at the mid and high doses and in hepatocellular tumors and thyroid follicular adenoma/cystadenoma and carcinoma in males at the high dose. The data suggest that the above effects could possibly be mediated by non-genotoxic mechanisms, the relevance of which to humans is not known.

The doses used in the mouse study may not have been high enough to fully characterize the carcinogenic potential of REMERON[™].

Mutagenesis

REMERON[™] was not mutagenic or clastogenic and did not induce general DNA damage as determined in several genotoxicity tests: Ames test, in vitro gene mutation assay in Chinese hamster V 79 cells, in vitro sister chromatid exchange assay in cultured rabbit lymphocytes, in vivo bone marrow micronucleus test in rats, and unscheduled DNA synthesis assay in HeLa cells.

Impairment of Fertility

In a fertility study in rats, Remeron[™] was given at doses up to 100 mg/kg (20 times the maximum recommended human dose (MRHD) on a mg/m² basis). Mating and conception were not affected by the drug, but estrous cycling was disrupted at doses that were 3 or more times the MRHD and pre-implantation losses occurred at 20 times the MRHD.

Pregnancy

Teratogenic Effects - Pregnancy Category C

Reproduction studies in pregnant rats and rabbits at doses up to 100 mg/kg and 40 mg/kg, respectively (20 and 17 times the maximum recommended human dose (MRHD) on a mg/m² basis, respectively), have revealed no evidence of teratogenic effects. However, in rats, there was an increase in post-implantation losses in dams treated with Remeron[™] (mirtazapine). There was an increase in pup deaths during the first 3 days of lactation and a decrease in pup birth weights.

The cause of these deaths is not known. These effects occurred at doses that were 20 times the MRHD, but not at 3 times the MRHD, on a mg/m² basis. There are no adequate and well controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers

It is not known whether mirtazapine is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when REMERON[™] (mirtazapine) Tablets are administered to nursing women.

Pediatric Use

Safety and effectiveness in children have not been established.

Geriatric Use

Approximately 190 elderly individuals (≥ 65 years of age) participated in clinical studies with Remeron. No unusual adverse age-related phenomena were identified in this group. Pharmacokinetic studies revealed a decreased clearance in the elderly. Caution is indicated in administering Remeron to elderly patients (see Clinical Pharmacology and Dosage and Administration).

ADVERSE REACTIONS

Associated with discontinuation of treatment

Approximately 16 percent of the 453 patients who received Remeron in US 6-week controlled clinical trials discontinued treatment due to an adverse experience, compared to 7 percent of the 361 placebo-treated patients in those studies. The most common events (≥1%) associated with discontinuation and considered to be drug related (i.e., those events associated with dropout at a rate at least twice that of placebo) included:

Common Adverse Events Associated with Discontinuation of Treatment in 6-Week US Remeron Trials		
Adverse Event	Percentage of Patients Discontinuing with Adverse Event	
	Remeron (n=453)	Placebo (n=361)
Somnolence	10.4%	2.2%
Nausea	1.5%	0%

Commonly Observed Adverse Events in US Controlled Clinical Trials

The most commonly observed adverse events associated with the use of REMERON™ (incidence of 5% or greater) and not observed at an equivalent incidence among placebo-treated patients (Remeron incidence at least twice that for placebo) were:

Common Treatment-Emergent Adverse Events Associated with the Use of Remeron in 6-Week US Trials		
Adverse Event	Percentage of Patients Reporting Adverse Event	
	Remeron (n=453)	Placebo (n=361)
Somnolence	54%	18%
Increased Appetite	17%	2%
Weight Gain	12%	2%
Dizziness	7%	3%

Adverse Events Occurring at an Incidence of 1% or More Among REMERON™ Treated Patients

The table that follows enumerates adverse events that occurred at an incidence of 1% or more, and were more frequent than in the placebo group, among Remeron-treated patients who participated in short-term U.S. placebo-controlled trials in which patients were dosed in a range of 5 to 60 mg/day. This table shows the percentage of patients in each group who had at least one episode of an event at some time during their treatment. Reported adverse events were classified using a standard COSTART-based dictionary terminology.

The prescriber should be aware that these figures cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those which prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other investigations involving different treatments, uses and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and non-drug factors to the side effect incidence rate in the population studied.

**INCIDENCE OF ADVERSE CLINICAL EXPERIENCES¹ (≥1%)
IN SHORT-TERM U.S. CONTROLLED STUDIES**

Body System Adverse Clinical Experience	Org 3770 (N=453)	Placebo (N=361)
Body as a Whole		
Asthenia	8%	5%
Flu Syndrome	5%	3%
Back Pain	2%	1%
Digestive System		
Dry Mouth	25%	15%
Increased Appetite	17%	2%
Constipation	13%	7%
Metabolic and Nutritional Disorders		
Weight Gain	12%	2%
Peripheral Edema	2%	1%
Edema	1%	0%
Musculoskeletal System		
Myalgia	2%	1%
Nervous System		
Somnolence	54%	18%
Dizziness	7%	3%
Abnormal Dreams	4%	1%
Thinking Abnormal	3%	1%
Tremor	2%	1%
Confusion	2%	0%
Respiratory System		
Dyspnea	1%	0%
Urogenital System		
Urinary Frequency	2%	1%

¹ Events reported by at least 1% of patients treated with Remeron (mirtazapine) are included, except the following events which had an incidence on placebo ≥ Remeron.

headache, infection, pain, chest pain, palpitation, tachycardia, postural hypotension, nausea, dyspepsia, diarrhea, flatulence, insomnia, nervousness, libido decreased, hypertension, pharyngitis, rhinitis, sweating, amblyopia, tinnitus, taste perversion.

ECG Changes

In an analysis of ECGs obtained in U.S. placebo-controlled clinical trials, REMERON[™] and placebo-treated patients had a similar incidence of abnormal changes from baseline at 6-8 weeks of approximately 3%. The abnormalities were generally not considered clinically significant.

Other Adverse Events Observed During the Premarketing Evaluation of REMERON[™]

During its premarketing assessment, multiple doses of REMERON[™] (mirtazapine) were administered to 2796 patients in clinical studies. The conditions and duration of exposure to mirtazapine varied greatly, and included (in overlapping categories) open and double-blind studies, uncontrolled and controlled studies, inpatient and outpatient studies, fixed dose and titration studies. Untoward events associated with this exposure were recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of untoward events into a smaller number of standardized event categories.

In the tabulations that follow, reported adverse events were classified using a standard COSTART-based dictionary terminology. The frequencies presented, therefore, represent the proportion of the 2796 patients exposed to multiple doses of Remeron who experienced an event of the type cited on at least one occasion while receiving Remeron. All reported events are included except those already listed in the previous table, those adverse experiences subsumed under COSTART terms that are either overly general or excessively specific so as to be uninformative, and those events for which a drug cause was very remote.

It is important to emphasize that, although the events reported occurred during treatment with Remeron, they were not necessarily caused by it.

Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse events are those occurring on one or more occasions in at least 1/100 patients; infrequent

adverse events are those occurring in 1/100 to 1/1000 patients; rare events are those occurring in fewer than 1/1000 patients. Only those events not already listed in the previous table appear in this listing. Events of major clinical importance are also described in the WARNINGS and PRECAUTIONS sections.

Body as a whole: frequent: malaise, abdominal pain, abdominal syndrome acute; infrequent: chills, fever, face edema, ulcer, photosensitivity reaction, neck rigidity, neck pain, abdomen enlarged; rare: cellulitis, chest pain substernal.

Cardiovascular System: frequent: hypertension, vasodilatation; infrequent: angina pectoris, myocardial infarction, bradycardia, ventricular extrasystoles, syncope, migraine, hypotension; rare: atrial arrhythmia, bigeminy, vascular headache, pulmonary embolus, cerebral ischemia, cardiomegaly, phlebitis, left heart failure.

Digestive System: frequent: vomiting, anorexia; infrequent: eructation, glossitis, cholecystitis, nausea and vomiting, gum hemorrhage, stomatitis, colitis, liver function tests abnormal; rare: tongue discoloration, ulcerative stomatitis, salivary gland enlargement, increased salivation, intestinal obstruction, pancreatitis, aphthous stomatitis, cirrhosis of liver, gastritis, gastroenteritis, oral moniliasis, tongue edema.

Endocrine System: rare: goiter, hypothyroidism.

Hemic and Lymphatic System: rare: lymphadenopathy, leukopenia, petechia, anemia, thrombocytopenia, lymphocytosis, pancytopenia.

Metabolic and Nutritional Disorders: frequent: thirst; infrequent: dehydration, weight loss; rare: gout, SGOT increased, healing abnormal, acid phosphatase increased, SGPT increased, diabetes mellitus.

Musculoskeletal System: frequent: myasthenia, arthralgia; infrequent: arthritis, tenosynovitis; rare: pathological fracture, osteoporosis fracture, bone pain, myositis, tendon rupture, arthrosis, bursitis.

Nervous System: frequent: hypesthesia, apathy, depression, hypokinesia, vertigo, twitching, agitation, anxiety, amnesia, hyperkinesia, paresthesia; infrequent: ataxia, delirium, delusions, depersonalization, dyskinesia, extrapyramidal

syndrome, libido increased, coordination abnormal, dysarthria, hallucinations, manic reaction, neurosis, dystonia, hostility, reflexes increased, emotional lability, euphoria, paranoid reaction; rare: aphasia, nystagmus, akathisia, stupor, dementia, diplopia, drug dependence, paralysis, grand mal convulsion, hypotonia, myoclonus, psychotic depression, withdrawal syndrome.

Respiratory System: frequent: cough increased, sinusitis; infrequent: epistaxis, bronchitis, asthma, pneumonia; rare: asphyxia, laryngitis, pneumothorax, hiccup.

Skin and Appendages: frequent: pruritus, rash; infrequent: acne, exfoliative dermatitis, dry skin, herpes simplex, alopecia; rare: urticaria, herpes zoster, skin hypertrophy, seborrhea, skin ulcer.

Special Senses: infrequent: eye pain, abnormality of accommodation, conjunctivitis, deafness, keratoconjunctivitis, lacrimation disorder, glaucoma, hyperacusis, ear pain; rare: blepharitis, partial transitory deafness, otitis media, taste loss, parosmia.

Urogenital System: frequent: urinary tract infection; infrequent: kidney calculus, cystitis, dysuria, urinary incontinence, urinary retention, vaginitis, hematuria, breast pain, amenorrhea, dysmenorrhea, leukorrhea, impotence, rare: polyuria, urethritis, metrorrhagia, menorrhagia, abnormal ejaculation, breast engorgement, breast enlargement, urinary urgency.

DRUG ABUSE AND DEPENDENCE

Controlled Substance Class

REMERON™ (mirtazapine) Tablets are not a controlled substance.

Physical and Psychologic Dependence

REMERON™ (mirtazapine) has not been systematically studied in animals or humans for its potential for abuse, tolerance or physical dependence. While the clinical trials did not reveal any tendency for any drug-seeking behavior, these observations were not systematic and it is not possible to predict on the basis of this limited experience the extent to which a CNS-active drug will be misused, diverted and/or abused once marketed. Consequently, patients should be evaluated

carefully for history of drug abuse, and such patients should be observed closely for signs of mirtazapine misuse or abuse (e.g., development of tolerance, incrementations of dose, drug-seeking behavior).

OVERDOSEAGE

Human Experience

There is very limited experience with REMERON[®] (mirtazapine) overdose. In premarketing clinical studies, there were eight reports of mirtazapine overdose alone or in combination with other pharmacological agents. The only drug overdose death reported while taking REMERON[®] (mirtazapine) Tablets was in combination with amitriptyline and chlorprohixene in a non-U.S. clinical study. Based on plasma levels, the REMERON[®] dose taken was 30-45 mg, while plasma levels of amitriptyline and chlorprohixene were found to be at toxic levels. All other premarketing overdose cases resulted in full recovery. Signs and symptoms reported in association with overdose included disorientation, drowsiness, impaired memory, and tachycardia. There were no reports of ECG abnormalities, coma or convulsions following overdose with REMERON[®] alone.

Overdose Management

Treatment should consist of those general measures employed in the management of overdose with any antidepressant. There are no specific antidotes for REMERON[®]. If the patient is unconscious, establish and maintain an airway to ensure adequate oxygenation and ventilation. Gastric evacuation either by the induction of emesis or lavage or both should be considered. Activated charcoal should also be considered in treatment of overdose. Cardiac and vital signs monitoring is recommended along with general symptomatic and supportive measures.

In managing overdosage, consider the possibility of multiple-drug involvement. The physician should consider contacting a poison control center for additional information on the treatment of any overdose.

DOSAGE AND ADMINISTRATION

Initial Treatment

The recommended starting dose for REMERON™ (mirtazapine) is 15 mg/day, administered in a single dose, preferably in the evening prior to sleep. In the controlled clinical trials establishing the antidepressant efficacy of Remeron, the effective dose range was generally 15-45 mg/day. While the relationship between dose and antidepressant response for REMERON™ has not been adequately explored, patients not responding to the initial 15 mg dose may benefit from dose increases up to a maximum of 45 mg/day. REMERON™ has an elimination half-life of approximately 20-40 hours, therefore, dose changes should not be made at intervals of less than one to two weeks in order to allow sufficient time for evaluation of the therapeutic response to a given dose.

Elderly and Patients with Renal or Hepatic Impairment

The clearance of mirtazapine is reduced in elderly patients and in patients with moderate to severe renal or hepatic impairment. Consequently, the prescriber should be aware that plasma mirtazapine levels may be increased in these patient groups compared to levels observed in younger adults without renal or hepatic impairment. (See Pharmacokinetics Subsection of CLINICAL PHARMACOLOGY).

Maintenance/Extended Treatment

There is no body of evidence available from controlled trials to indicate how long the depressed patient should be treated with Remeron. It is generally agreed, however, that pharmacological treatment for acute episodes of depression should continue for up to six months or longer. Whether the dose of antidepressant needed to induce remission is identical to the dose needed to maintain euthymia is unknown.

Switching Patients to or from a Monoamine Oxidase Inhibitor

At least 14 days should elapse between discontinuation of an MAOI and initiation of therapy with REMERON™. In addition, at least 14 days should be allowed after stopping REMERON™ before starting an MAOI.

HOW SUPPLIED

REMERON™ (mirtazapine) Tablets are supplied as:

15 mg Tablets - oval, scored, yellow, coated, with "Organon" embossed on one side and "TZ3" on the other side.

Bottles of 30	NDC# 0052-0105-30
Bottles of 100	NDC# 0052-0105-91
Bottles of 500	NDC# 0052-0105-95
Unit Dose, Box of 100	NDC# 0052-0105-90*

30 mg Tablets - oval, scored, red-brown, coated, with "Organon" embossed on one side and "TZ5" on the other side.

Bottles of 30	NDC# 0052-0107-30
Bottles of 100	NDC# 0052-0107-91
Bottles of 500	NDC# 0052-0107-95
Unit Dose, Box of 100	NDC# 0052-0107-90

*Unit dose packs are provided as a blisterpack with 10 strips, each of which contain 10 tablets.

Store at controlled Room Temperature
20°-25°C (68° - 77°F) [See USP]

Dispense in a tight, light resistant container.

Caution: Federal law prohibits dispensing without prescription.

Doc LABMRTDP.AP1

**Memorandum Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research**

DATE: June 11, 1996

FROM: Paul Leber, M.D.
Director,
Division of Neuropharmacological Drug Products
HFD-120

SUBJECT: Remeron (mirtazapine) NDA 20-415

TO: File NDA 20-415
 &
 Robert Temple, M.D.
 Director, Office of New Drug Evaluation 1

This memorandum notes for the file my endorsement of the recommendation of the Division's Review Team that Organon's NDA 20-415 for Remeron be approved. An explication of my views regarding the probity of the evidence available to support a conclusion that mirtazapine is safe for use and effective in use is provided in my memorandum of January 8, 1996.

One aspect of the final approval action deserves comment. The approvable action letter issued on January 26, 1996 conditioned final approval of the NDA upon the sponsor's agreement to adopt, verbatim, the draft product labeling provided as an attachment to the approvable letter. A prominent feature of that labeling was a bolded boxed warning detailing the association between Remeron's use and the occurrence of agranulocytosis.

In its response to the approvable action letter, the firm argued vigorously against a boxed warning. While the use of a boxed warning has regulatory implications vis a vis advertising, I am not persuaded the boxed format, per se, makes a substantive difference in regard to either the informational content of the labeling or the strength of the warning provided to potential prescribers (i.e., I doubt that prescribers will be aware of the import of a boxed vs. a non-boxed warning). In short, I do not find a boxed warning a sine qua non of Remeron's marketing and, accordingly, I can endorse the review team's recommendation (see Dr. Laughren's May 20, 1996 approval recommendation memorandum) that the product be approved under the labeling attached to the approval action letter being forwarded to the Office for signature.

Recommendation:

Issue the approval letter.

A handwritten signature in black ink, consisting of a large, stylized 'P' followed by a horizontal line and a small flourish.

Paul Leber, M.D.
June 11, 1996

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: May 20, 1996

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

SUBJECT: Recommendation for Approval Actior for
Remeron (mirtazapine) for depression

TO: File NDA 20-415
[Note: This overview should be filed with the 3-15-96
submission.]

1.0 BACKGROUND

In our 1-26-96 approvable letter, we requested a safety update, a foreign regulatory update, and a commitment to conduct studies addressing the following clinical issues: relapse prevention, pediatric depression, dose response for effectiveness, and dose response and time course for sedative effects. In the pharm/tox area, we notified the sponsor of our intention to label Remeron as Pregnancy Category C and we also asked for a 3-month mouse dietary administration study to address the concerns about failure to reach MTD in the mouse carcinogenicity study. In the biopharmaceutics area, we requested data pertinent to the issue of P450 metabolism. We also attached our proposal for labeling. In subsequent letters we asked for a literature update (4-19-96) and a more detailed regulatory status update including both foreign labeling and a comment on any negative actions by foreign regulatory agencies (4-22-96). Organon responded to all of the issues in their 3-15-96 and 5-10-96 submissions.

We met with the sponsor on 4-23-96 to discuss labeling. On 5-6-96 we faxed the sponsor an alternative version of labeling. In their 5-10-96 submission, the sponsor accepted our 5-6-96 labeling draft with only minor changes which we consider acceptable.

The remaining materials in these submissions have been reviewed by the pertinent disciplines and it is agreed that the sponsor has now met the requirements for final approval.

2.0 SAFETY UPDATE

The safety update included information on serious events from 6 ongoing foreign clinical trials covering a period of 1-31-95 through 10-31-95. There were no deaths and only 2 serious events, neither of which could be reasonably attributed to mirtazapine.

We had also asked for an update on the postmarketing experience with mirtazapine and the sponsor indicated that there had been postmarketing spontaneous reports for a total of 24 patients, all from the Netherlands. None of these reports included new or unusual findings that would necessitate further labeling changes. Of note, there were no reports of agranulocytosis.

3.0 WORLD LITERATURE UPDATE

The sponsor's literature update covered the period of 1994 to the present. They warranted that their search of the literature revealed no findings that would adversely affect the conclusions about mirtazapine's safety. Dr. Mosholder reached a similar conclusion.

4.0 FOREIGN REGULATORY UPDATE

To my knowledge, Remeron is approved in 12 countries worldwide, however, it is still marketed only in the Netherlands. The sponsor warranted in the 5-10-96 submission that no negative regulatory actions have been taken with regard to Remeron.

The package inserts from countries where Remeron has been approved were reviewed by Dr. Mosholder, and he concluded that no important new information regarding the safety of Remeron was revealed. In general, our proposed labeling tends to be stronger than that approved in foreign countries.

5.0 REQUESTS FOR ADDITIONAL CLINICAL TRIALS

5.1 Exploration for Dose Response for Effectiveness

The sponsor has agreed to expand their planned phase 4 dose response study focusing on somnolence to include efficacy assessments.

5.2 Exploration of Dose Response and Time Course for Sedative Effects of Mirtazapine

The sponsor has proposed a phase 4 study that should adequately explore the question of dose response for somnolence.

5.3 Pediatric Depression Studies

It was mutually agreed that it would not be necessary at this time to study mirtazapine in pediatric patients.

5.4 Long-Term Effectiveness Studies

The sponsor has committed to conducting a phase 4 study to adequately address the question of long term effectiveness.

6.0 CHEMISTRY

In our 1-26-96 approvable letter, we noted that methods validation had not yet been completed and noted a 24 month limit on the expiry date.

The methods validation has now been successfully completed.

We have also reached agreement with Organon on the expiration date. They must specify 24 months at the present time, however, they may automatically extend the date as they accumulate 30-36 month data and inform us after the fact.

7.0 PHARMACOLOGY

The sponsor has agreed to a classification of mirtazapine as pregnancy Category C.

In our 1-26-96 approvable letter, we expressed concern about the MTD in the 18-month mouse carcinogenicity study, and asked for a commitment to do a 3-month dietary administration study in phase 4. The sponsor has agreed to initially perform a 2-week pilot dietary study and discuss the results with us before proceeding with the larger 3-month study. The Pharmacology Group considers this an acceptable response.

8.0 BIOPHARMACEUTICS

In our 1-26-96 approvable letter, we had asked for either additional in vitro metabolism work or alternatively a more complete report on work already accomplished. The sponsor provided a report on work mentioned at the 10-16-96 PDAC meeting, and we have generally agreed that these data adequately address this request for in vitro data. However, draft labeling, while acknowledging the absence of any in vitro findings suggestive of an important inhibitory effect of mirtazapine, also acknowledges the lack of in vivo data as a basis for making any definitive statements about the risk of inhibitory effects.

The sponsor accepted our proposed dissolution method and specifications.

9.0 LABELING AND APPROVAL LETTER

Labeling

Organon proposed numerous changes to the labeling for Remeron, many of which we found acceptable, while others were the subject of debate at our 4-23-96 meeting. I will comment here only on the labeling issues that were a matter of particular controversy:

Black Box for Agranulocytosis:

In our original labeling proposal, we had both bolded and boxed the agranulocytosis statement to emphasize the importance of this signal. This issue was discussed but left unresolved at our 4-23-96 labeling meeting with the sponsor. The sponsor argued against the need for a box, suggesting that the signal was not strong enough to justify a box and furthermore suggested that the box is not consistently applied across approved labeling. The sponsor also argued for modified language, in particular for the deletion of a point estimate and confidence limits for the agranulocytosis risk and the addition of the reassuring data from the Netherlands postmarketing experience. In his 5-16-96 review, Dr. Mosholder argued that the box should remain since this would limit the promotion of the drug and therefore limit the possibility of physicians overlooking this important concern.

I am willing to yield on this issue for several reasons. While a box may limit to some extent the sponsor's ability to promote a product, it isn't clear to what extent such an effect on promotion is linked to whether or not physicians will attend to a particular risk. In fact I believe that we don't know whether or not a box is any more effective than a bolded warning in directing physicians' attention to an important concern. Furthermore, I believe the sponsor is probably correct in suggesting that the box is not applied in a consistent manner across all drugs.

What I feel is likely more important than the box is the content of the Warning statement. They argued for a weaker statement not including an actual risk estimate with confidence limits, and alternatively, proposed including a description of the negative postmarketing experience in the Netherlands. Given the fact that 10% or less of adverse events are voluntarily reported, the finding of no cases of agranulocytosis among approximately 10,000 exposed patients is not inconsistent with the risk estimate of 1 per 1000. Since the sponsor is now willing to accept our stronger language, I am comfortable with a bolded warning rather than a boxed and bolded warning.

Precautions Statement for Somnolence:

In our original labeling proposal, we had included a statement that several motor vehicle accidents (MVAs) had been reported in association with mirtazapine use, including two that were attributed by either the patient or physician to mirtazapine. The sponsor argued that all sedating drugs have this potential, yet are not linked specifically in labeling to the possibility of MVAs. We subsequently agreed to remove this statement if the remainder of the Precautions statement could be bolded. The sponsor argued against this as well, and submitted data from the Statistical Abstracts of the United States, suggesting that the finding of 4 MVAs among approximately 3000 patients in the premarketing database was not unexpected. While it's difficult to compare the clinical trials experience with the Statistical Abstracts data, I think it's true that we have not applied the same standard to other NDAs, in the sense of looking specifically for MVAs. I am comfortable with the language proposed by the sponsor, especially since the Information for Patients statement and other sections of labeling make it clear that mirtazapine is a very sedating drug. Physicians who read the labeling will not miss this point.

Statement Regarding Increased Clearance in Smokers:

We had originally proposed a statement under Pharmacokinetics suggesting a 30% decrease in clearance among smokers compared to nonsmokers. This statement was based on a meta-analysis done by the Biopharmaceutics reviewer. The sponsor expressed concern about the relevance of this finding. In looking at the individual data, extensive overlap in clearance was apparent between the smokers and nonsmokers, despite the mean difference between the groups. That finding, along with the fact that individual patients would typically be titrated to their best dose, leads me to agree that the finding is not of much direct clinical value and I don't object to its deletion.

Characterization of Mirtazapine's Pharmacology:

There was much discussion of the language in the pharmacodynamics section regarding the best way to characterize the pharmacology of mirtazapine. In the end, I think the mutually agreed upon language fairly describes the pharmacology of this drug without speculating about its effects and about which of its effects is critical in explaining its apparent antidepressant actions.

Approval Letter

Dr. Mosholder has suggested adding to the approval letter requests that the sponsor submit any spontaneous reports of hematologic abnormality and any cases of hepatic toxicity as 15 day reports rather than in periodic reports to facilitate our efficient evaluation of these concerns, and I agree with this proposal.

10.0 CONCLUSIONS AND RECOMMENDATIONS

I believe that Organon has submitted sufficient data to support the conclusion that Mirtazapine is effective and acceptably safe in the treatment of depression. I recommend that we issue the attached approval letter with the mutually agreed upon final labeling.

CC:

Orig NDA 20-415

HFD-120

HFD-120/TLaughren/PLeber/AMosholder/PDavid

HFD-100/RTemple

DOC: MEMMRTDP.AP1

JAN 26 1996

NDA 20-415

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

Dear Mr. Mayo:

Please refer to your New Drug Application (and your resubmission dated January 26, and received on January 30, 1995) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Remeron™ (Mirtazapine) 15 and 30 mg tablets.

We also acknowledge receipt of your additional communications (see ATTACHMENT 1).

We have completed the review of this application as submitted with draft labeling, and it is approvable. Before the application may be approved, however, it will be necessary for you to respond to the following items:

CLINICAL

1. Labeling

Accompanying this letter (ATTACHMENT 2) is the Agency's proposal for the labeling of Remeron™. We believe it presents a fair summary of the information available on the benefits and risks of mirtazapine. Please use the proposed text verbatim.

We have proposed a number of changes to the draft labeling submitted in your August 21, 1995 labeling amendment, and explanations for these changes are provided in the bracketed comments embedded within the proposed text. Division staff would be happy to discuss these proposed changes in detail, and we would be happy to meet with you to discuss any disagreements you might have with any part of the proposed labeling format or content.

2. Safety Update

Our assessment of the safety of mirtazapine is based on our review of all safety information provided in your original and subsequent submissions, including your safety update (July 28, 1995 amendment). This original review was based on an integrated database comprising studies completed prior to December, 1993, for which no more data will be forthcoming, and on any additional serious events reported from a completed European study (86017) and from five ongoing foreign studies, with a cutoff date of approximately July, 1995. Please provide a final serious events update to include serious adverse events up to a more recent cutoff date.

In addition, please provide an updated postmarketing adverse event report from the Netherlands and any other countries where Remeron™ is now available. In order to help us in interpreting this information, please provide details on the methodology for postmarketing surveillance in those countries for which such reports are available. In particular, it would be helpful to know what information is available regarding the numbers of patients exposed and the extent of exposure, how this information is determined, what mechanism is used for reporting and whether or not follow-up on cases is feasible.

3. Regulatory Status Update

Please provide any new information on the regulatory status of mirtazapine worldwide, i.e., information available subsequent to the regulatory status update provided in your September 26, 1995 amendment.

4. Exploration of Dose Response for Effectiveness

While your development program for mirtazapine has identified an effective dose range for this drug, it has not adequately addressed dose response within this range. Consequently, we ask that you commit to conducting, subsequent to approval as a Phase 4 commitment, additional studies to properly explore the 15-45 mg range. The Division will be happy to collaborate with your clinical and statistical staff in the design of such a program.

5. Exploration of Dose Response and Time Course for Sedative Effects of Mirtazapine

One of the more troublesome of the common adverse events associated with mirtazapine use is its somnolent properties. What is unknown from the available data is the dose dependency for this event and whether or not and to what extent there may be adaptation. This is a sufficiently important clinical concern that we ask your commitment to conducting, subsequent to approval, a study that provides data pertinent to this issue. It may be possible to combine this effort and an exploration of dose/response for efficacy into one study. Again, the Division will be happy to collaborate with your clinical and statistical staff in the design of such a program.

6. Pediatric Depression Studies

Since it is likely that mirtazapine, once marketed, will be used in children and adolescents with depression, we ask that you commit to conducting, subsequent to approval as a Phase 4 commitment, studies in these populations in order to provide the safety and efficacy data needed to support such use. A useful starting point would be to obtain some pharmacokinetic data in depressed children and adolescents. The Division will be happy to collaborate with your clinical and statistical staff in your design of such a program.

7. Long-Term Efficacy Studies

Although your NDA for Remeron™ documents the effectiveness of mirtazapine as a treatment of acute depressive illness over an interval of 6 weeks, it fails to provide

necessary to sustain its antidepressant effects over the full duration (presumed to be 6 months to a year) of an acute depressive episode. However, because it is widely assumed that continued treatment of symptomatically remitted patients reduces their risk of relapse, the proposed labeling for Remeron™ recommends that treatment be continued, presumably at the same doses as those used to induce remission, for intervals of several months or longer following the acute episode for which treatment was initiated. These labeling recommendations notwithstanding, the conditions of extended use that maximally decrease the risk of relapse are unknown. Accordingly, we ask for your commitment to conduct, subsequent to approval as a Phase 4 commitment, a controlled trial to evaluate the conditions affecting mirtazapine's capacity to reduce the risk of relapse in acutely remitted patients. Because the methods for conducting such a study of the type described are still in evolution, the Division will be happy to collaborate with your clinical and statistical staff should questions concerning its design and/or conduct arise.

PHARMACOLOGY

1. Pregnancy Category C

The segment I and II reproduction studies in rats revealed a decrease in pup survival, and also a decrease in pup weights (segment III only). In the segment II study (teratology) there was an increased incidence of post-implantation loss. Because it cannot be determined whether or not these findings were related to effects of the drug on the developing fetus in utero or were secondary to postnatal drug effects on the dams and/or pups, we have labeled Remeron™ pregnancy category C.

2. Mouse carcinogenicity study

The CDER Carcinogenicity Assessment Committee (CAC) voted that a maximum tolerated dose (MTD) was not achieved in the 18 month mouse carcinogenicity study, and concluded that exposure data are needed before a determination about the adequacy of the study may be made. We request, as a Phase 4 commitment, that you agree to conduct a three month dietary administration study in mice to address this issue. The study should be designed to examine the plasma AUC's of parent drug and all major metabolites, particularly those found in both humans and mice. Doses should include the high dose of 200 mg/kg used in the carcinogenicity study and also two or more higher doses, chosen to attempt to determine an actual MTD. It is hoped that the information obtained from such a study will permit us to make a decision about whether or not the high dose of 200 mg/kg provided adequate exposure of drug and metabolites relative to human exposure to consider the study valid. It should also provide us with information about what fraction of an MTD was actually achieved. Depending upon the outcome of that three month study, additional Phase 4 studies may be required. Our staff will be happy to assist you in the design of this study if you wish.

MANUFACTURING AND CONTROLS**1. 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. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

2. Expiration Date

Please note that, at this time, we are only approving a 24-month expiry date for the drug product based on the 18-month stability data which was provided.

BIOPHARMACEUTICS**1. Phase 4 Commitments**

We request that you perform in vitro enzymatic experiments on mirtazapine with other inhibitors or substrates of CYP1A2 (e.g., theophylline and fluvoxamine), CYP2D6 (e.g., tricyclic antidepressants and selective serotonin reuptake inhibitors), and CYP3A (e.g., ketoconazole and erythromycin), and submit these results to the Agency. It is possible that you have already conducted studies that will adequately address these issues, e.g., some pertinent in vitro data were presented in a preliminary manner at the October 16, 1995 meeting of the Psychopharmacological Drugs Advisory Committee meeting. However, we ask that you submit a more complete report on these studies.

2. Dissolution Specification

We ask that you agree to the following recommendation by the Division of Biopharmaceutics for a dissolution method and specification for all tablet strengths:

Apparatus:

Paddle Speed:

Medium:

Specification:

Additionally, please provide the Agency with a proposed completion date for all Phase 4 commitments which you agree to conducting.

Please submit sixteen copies of the printed labeling, ten of which are individually mounted on heavy weight paper or similar material.

In addition, please submit three copies of the introductory promotional material 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 material and the package insert directly to:

Food and Drug Administration
Division of Drug Marketing, Advertising and Communications,
HFD-40
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 such action FDA may take action to withdraw the application.

Should you have any questions, please contact:

Paul David, R.Ph.
Regulatory Management Officer
Telephone: (301) 594-2777

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

Sincerely yours,

A handwritten signature in black ink, appearing to read "R Temple 1/26/82".

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

ATTACHMENTS

ATTACHMENT 1

NDA 20-415 Remeron™ (Mirtazapine) Tablets

Amendments and Correspondence submitted to NDA since original resubmission:

February 13, 1995
April 4, 1995
May 1, 1995
May 8, 1995(2)
May 25, 1995
June 29, 1995
July 20, 1995
August 8, 1995
August 28, 1995
September 13, 1995
September 28, 1995
October 19, 1995
November 8, 1995

February 17, 1995(2)
April 5, 1995
May 2, 1995
May 18, 1995
June 22, 1995
July 3, 1995
July 27, 1995
August 10, 1995
September 11, 1995
September 14, 1995
October 5, 1995
October 30, 1995

February 27, 1995
April 19, 1995(2)
May 3, 1995
May 19, 1995(2)
June 26, 1995
July 17, 1995
July 28, 1995(2)
August 21, 1995
September 12, 1995
September 26, 1995
October 12, 1995
November 6, 1995(2)

ATTACHMENT 2

DRAFT LABELING PROPOSAL

Note: Brackets [] embedded within the text that follows include comments and explanations concerning the proposed draft labeling. For some sections, few changes were proposed, while others required extensive modification. This revision is based on the version of labeling submitted in the August 21, 1995 original submission. If you feel that further revisions are necessary to this draft, please use this exact document as the starting document. Please use the 'strikeout' font to indicate the material you wish to delete and the 'redline' font to indicate the material you wish to add.

REMERON™ (mirtazapine) Tablets

DESCRIPTION

[We have made a slight modification to the first sentence of the first paragraph in this section, since it suggested that Remeron is a unique antidepressant. Rather, we have clarified that the chemical structure is unique. We have additionally included a statement specifying that Remeron is a racemic mixture.]

REMERON™ (mirtazapine) is an antidepressant for oral administration with a tetracyclic chemical structure unrelated to selective serotonin reuptake inhibitors, tricyclics or monoamine oxidase inhibitors (MAOI). Mirtazapine belongs to the piperazino-azepine group of compounds. It is designated 1,2,3,4,10,14b-hexahydro-2-methylpyrazino [2,1-a] pyrido [2,3-c] benzazepine and has the empirical formula of C₁₇H₁₉N₃. Its molecular weight is 265.36. The structural formula is the following and it is the racemic mixture:

[Insert structural formula here.]

Mirtazapine is a white to creamy white crystalline powder which is slightly soluble in water.

REMERON™ is supplied for oral administration as scored film-coated tablets containing 15 or 30 mg of mirtazapine. Each tablet also contains corn starch, hydroxypropyl cellulose,

magnesium stearate, colloidal silicon dioxide, lactose and other inactive ingredients.

CLINICAL PHARMACOLOGY

Pharmacodynamics

[We have made several modifications to this section.

-Our current approach to this subsection of antidepressant labeling is to acknowledge that the pharmacological basis for the antidepressant action of any of these drugs is not known with any certainty. Alternatively, we believe it is most informative to neutrally describe the pharmacology of mirtazapine, except in those instances when the linkage to clinical effects is adequately known, e.g., histamine antagonism for sedation and α_1 adrenergic antagonism for orthostatic effects. We have also deleted the discussion of enantiomer specific effects since the data supporting those statements are complicated; a much longer discussion would be needed to adequately address this issue, and there would be no clear clinical relevance for such a discussion.

-We have deleted the qualifier "initial" to sedative, since the somnolent effects of mirtazapine appear to persist in many patients.

-We have added a reference to the α_1 adrenergic antagonist effect, as a probable explanation for the hypotensive effects observed in phase 1 studies and dizziness observed in phase 2-3 studies.

-We have deleted the reference to anxiolytic effects, since mirtazapine has not been developed as an anxiolytic and its effects on anxiety symptoms have been addressed more appropriately in the Clinical Trials subsection.

-The references to the absence of anticholinergic side effects and cardiovascular effects have been deleted, since these issues are more appropriately addressed in the Adverse Reactions section. However, in this regard, we have noted the moderate antimuscarinic effect of Remeron.

-The reference to sleep effects has been deleted from this section, since the clinical effects on sleep disturbance in association with depression have been more appropriately addressed in the Clinical Trials subsection.]

The mechanism of action of REMERON™ (mirtazapine), as with other antidepressants, is unknown.

Preclinical studies have shown that mirtazapine acts as an antagonist at central presynaptic α_2 adrenergic inhibitory autoreceptors, an action that is postulated to result in an increase in central noradrenergic activity.

Mirtazapine is a potent antagonist of 5-HT₂ and 5-HT₁ receptors.

Mirtazapine is a potent antagonist of histamine (H₁) receptors, a property that may explain the sedative effects seen in patients receiving this drug.

Mirtazapine is a moderate peripheral α_1 adrenergic antagonist, a property that may explain orthostatic hypotension and dizziness reported in association with its use.

Mirtazapine is a moderate antagonist at muscarinic receptors.

Pharmacokinetics

[We have made numerous changes in the organization and content of this subsection.]

REMERON™ (mirtazapine) is rapidly and completely absorbed following oral administration and has a half-life of about 20-40 hours. Peak plasma concentrations are reached within about 2 hours following an oral dose. The presence of food in the stomach has a minimal effect on both the rate and extent of absorption and does not require a dosage adjustment.

Mirtazapine is extensively metabolized by cytochrome P450 enzymes, primarily 2D6 and 1A2 and to a lesser extent 2C9 and 3A, and has an absolute bioavailability of about 50%. It is eliminated predominantly via urine (75%) with 15% in feces. Major pathways of biotransformation are demethylation and hydroxylation followed by glucuronide conjugation. Several unconjugated metabolites possess pharmacological activity but are present in the plasma at very low levels. The (-) enantiomer has an elimination half-life that is approximately twice as long as the (+) enantiomer and therefore achieves plasma levels that are about three times as high as that of the (+) enantiomer.

Plasma levels are linearly related to dose over a dose range of 15 to 80 mg. The mean elimination half-life of mirtazapine after oral administration ranges from approximately 20-40 hours across age and gender subgroups, with females of all ages exhibiting significantly longer elimination half-lives than males (mean half-life of 37 hours for females vs 26 for males). Steady state plasma levels of mirtazapine are attained within 5 days, with about 50% accumulation (accumulation ratio = 1.5).

Mirtazapine is approximately 85% bound to plasma proteins over a concentration range of 0.01 to 10 µg/mL.

Population Subgroups

Liver Disease - Following a single 15 mg oral dose of mirtazapine, the oral clearance of mirtazapine was decreased by approximately 30% in hepatically impaired patients compared to subjects with normal hepatic function. Caution is indicated in administering REMERON™ to patients with compromised hepatic function (see Precautions and Dosage and Administration).

Renal Disease - Following a single 15 mg oral dose of mirtazapine, patients with moderate [glomerular filtration rate (GFR) = 11-39 mL/min/1.73 m²] and severe [GFR < 10 mL/min/1.73 m²] renal impairment had reductions in mean oral clearance of mirtazapine of about 30% and 50%, respectively, compared to normal subjects. Caution is indicated in administering REMERON™ to patients with compromised renal function (see Precautions and Dosage and Administration).

Elderly Patients - Following oral administration of mirtazapine 20 mg/day for 7 days to subjects of varying ages (range, 25-74), oral clearance of mirtazapine was reduced in the elderly compared to the younger subjects. The differences were most striking in males, with a 40% lower clearance in elderly males compared to younger males, while the clearance in elderly females was only 10% lower compared to younger females. Caution is indicated in administering REMERON™ to elderly patients (see Precautions and Dosage and Administration).

Smokers - Cigarette smoking increased the mean oral clearance of mirtazapine by about 30%.

Clinical Trials Showing Effectiveness

[Consistent with recently approved antidepressant products, we have added this subsection to describe in some detail the clinical trials supporting the effectiveness claim.]

The efficacy of REMERON™ (mirtazapine) as a treatment for depression was established in four placebo-controlled, 6-week trials in adult outpatients meeting DSM-III criteria for major depression. Patients were titrated with mirtazapine from a dose range of 10 mg up to 35 mg/day. Overall, these studies demonstrated mirtazapine to be superior to placebo on at least three of the following four measures: 21-Item Hamilton Depression Rating Scale (HDRS) total score; HDRS Depressed Mood Item; CGI Severity score; and Montgomery and Asberg Depression Rating Scale (MADRS). Significant differences were also found for certain factors of the HDRS (e.g., anxiety/somatization factor and sleep disturbance factor). The mean mirtazapine dose for patients who completed these four studies ranged from 21 to 32 mg/day. A fifth study of similar design utilized a higher dose (up to 50 mg) per day and also showed effectiveness.

Examination of age and gender subsets of the population did not reveal any differential responsiveness on the basis of these subgroupings.

INDICATIONS AND USAGE

[We have made a number of modifications to this section:

- We have changed the language for the claim to that currently used for antidepressants.

- We have added a reference to the Clinical Pharmacology subsection for details regarding the clinical trials supporting the claim.

- While DSMIII criteria were used in the conduct of your trials, we nevertheless think it would be appropriate to use the currently accepted definition of major depression, i.e., DSMIV.

- We have deleted the statement regarding anxiety reduction, since the effect on anxiety associated with depression has been more appropriately addressed in the Clinical Trials subsection.

- We have added a statement acknowledging that mirtazapine has not been adequately studied in depressed inpatients.

-Finally, since we disagree that you have provided adequate data pertinent to the question of long-term efficacy, we have added a statement noting that mirtazapine has not been adequately studied with regard to long-term efficacy or relapse prevention.

REMERON™ (mirtazapine) Tablets are indicated for the treatment of depression.

The efficacy of REMERON™ in the treatment of depression was established in six week controlled trials of outpatients whose diagnoses corresponded most closely to the Diagnostic and Statistical Manual of Mental Disorders - 3rd edition (DSM-III) category of major depressive disorder (see CLINICAL PHARMACOLOGY).

A major depressive episode (DSM-IV) implies a prominent and relatively persistent (nearly every day for at least 2 weeks) depressed or dysphoric mood that usually interferes with daily functioning, and includes at least five of the following nine symptoms: depressed mood, loss of interest in usual activities, significant change in weight and/or appetite, insomnia or hypersomnia, psychomotor agitation or retardation, increased fatigue, feelings of guilt or worthlessness, slowed thinking or impaired concentration, a suicide attempt or suicidal ideation.

The antidepressant effectiveness of REMERON™ (mirtazapine) in hospitalized depressed patients has not been adequately studied.

The effectiveness of REMERON™ in long-term use, that is, for more than 6 weeks, has not been systematically evaluated in controlled trials. Therefore, the physician who elects to use REMERON™ for extended periods should periodically evaluate the long-term usefulness of the drug for the individual patient.

CONTRAINDICATIONS

REMERON™ (mirtazapine) Tablets are contraindicated in patients with a known hypersensitivity to mirtazapine.

WARNINGS

Agranulocytosis

[We believe a rate of about 0.1% agranulocytosis requires a bolded boxed warning to emphasize the importance of this signal. Additionally, we have modified this statement by deleting the reference to the imipramine case. There are not adequate data in your database to make comparisons between mirtazapine and other antidepressants with regard to incidence of severe neutropenia and agranulocytosis. Rather, the point of this warning is to alert clinicians to the possibility of these serious events occurring in association with the use of mirtazapine. We have also added more details regarding mirtazapine to more fully describe the observed findings.]

In premarketing clinical trials, two (one with Sjögren's Syndrome) out of 2,796 patients treated with REMERON™ (mirtazapine) Tablets developed agranulocytosis [absolute neutrophil count (ANC) < 500/mm³ with associated signs and symptoms, e.g., fever, infection, etc.] and a third patient developed severe neutropenia [ANC < 500/mm³ without any associated symptoms]. For these three patients, onset of severe neutropenia was detected on days 9, 17, and 61 of treatment, respectively. All three patients recovered after Remeron was stopped. These three cases yield a crude incidence of severe neutropenia (with or without associated infection) of approximately 1.1 per thousand patients exposed, with a very wide 95% confidence interval, i.e., 2.2 cases per 10,000 to 3.1 cases per 1000. If a patient develops a sore throat, fever, stomatitis or other signs of infection, along with a low WBC count, treatment with REMERON™ should be discontinued and the patient should be closely monitored.

MAO Inhibitors

[We have made a minor editorial change to this statement, and we have added examples of the actual findings reported for other antidepressants. In keeping with recent labeling practice regarding this warning, we have added bold print for emphasis.]

In patients receiving other antidepressants in combination with a monoamine oxidase inhibitor (MAOI) and in patients who have recently discontinued an antidepressant drug and then are started on an MAOI, there have been reports of serious, and sometimes fatal, reactions, e.g., including nausea, vomiting, flushing, dizziness, tremor, myoclonus, rigidity, diaphoresis, hyperthermia, autonomic instability with rapid fluctuations of vital signs, seizures, and mental status changes ranging from agitation to coma. Although there are no human data pertinent to such an interaction with REMERON™, it is recommended that REMERON™ not be used in combination with an MAOI, or within 14 days of initiating or discontinuing therapy with an MAOI.

PRECAUTIONS

General

Somnolence

[We have modified this statement:

- We have added data for the control groups for comparison.
- We have added data on dropouts for somnolence.
- We have noted the occurrence of motor vehicle accidents attributed to Remeron, since this may be a measure of the severity of this adverse event in some patients.
- We don't believe that adequate data pertinent to the question of tolerance have been collected, consequently, we have simply noted that fact.]

In U.S. controlled studies, somnolence was reported in 56% of patients treated with REMERON™ (mirtazapine), compared to 18% for placebo and 60% for amitriptyline. In a pooled analysis of all premarketing US studies, somnolence resulted in discontinuation for 10.8% of Remeron treated patients, compared to 2.5% for placebo. Several patients treated with Remeron experienced motor vehicle accidents, which in two cases were attributed to the severe somnolent effects of Remeron. It is unclear whether or not tolerance develops to the somnolent effects of Remeron. Because of Remeron's potentially significant effects on impairment of performance, patients should be cautioned about engaging in activities requiring alertness until they have been able to assess the drug's effect on their own psychomotor performance (see Information for Patients).

Dizziness

[We have modified this statement:

- We have added data for the control groups for comparison.
- We don't believe that adequate data pertinent to the question of tolerance have been collected, consequently, we have simply noted that fact.]
- We believe there is a link between the orthostatic hypotension observed in ph 1 studies and the dizziness observed in ph 2-3 studies that needs to be acknowledged here. Consequently, we have noted this likely connection, and cautioned about the use of Remeron in patients likely to be vulnerable to adverse effects of lowered blood pressure.]

In U.S. controlled studies, dizziness was reported in 7% of patients treated with REMERON™ (mirtazapine), compared to 3% for placebo and 14% for amitriptyline. It is unclear whether or not tolerance develops to the dizziness observed in association with the use of Remeron. While the orthostatic hypotension observed in early clinical pharmacology trials with Remeron was not frequently observed in later clinical trials, the dizziness observed in association with mirtazapine use in these later trials was likely a manifestation of the same pharmacological basis for the orthostatic hypotension, i.e., probably α_1 antagonism. Thus, the prescriber should be aware that there is some risk of postural hypotension in association with mirtazapine use. REMERON™ 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).

Increased Appetite/Weight Gain

[[We have modified this statement:

- We have replaced the data provided in your draft of labeling with data that we feel are more pertinent, including the proportions of patients dropping out for weight gain.
- We have added data for the control groups for comparison.]

In US controlled studies, appetite increase was reported in 17% of patients treated with REMERON™ (mirtazapine), compared

to 2% for placebo and 6% for amitriptyline. In these same trials, weight gain of $\geq 7\%$ of body weight was reported in 7.5% of patients treated with mirtazapine, compared to 0% for placebo and 5.9% for amitriptyline. In a pooled analysis of premarketing US studies, weight gain resulted in discontinuation for 8.2% of mirtazapine treated patients, compared to 0.3% for placebo.

Cholesterol/Triglycerides

[We have modified this statement:

-We have replaced data suggested in your proposed labeling with data we feel are more pertinent.

-We have added data for the control groups for comparison.

-We have also added definitions of what is meant by clinically significant.]

In U.S. controlled studies, nonfasting cholesterol increases to $\geq 20\%$ above the upper limits of normal were observed in 15% of patients treated with REMERON[™] (mirtazapine), compared to 7% for placebo and 8% for amitriptyline. In these same studies, nonfasting triglyceride increases to ≥ 500 mg/dL were observed in 6% of patients treated with mirtazapine, compared to 3% for placebo and 3% for amitriptyline.

Transaminase Elevations

[We have slightly modified this statement.]

Clinically significant ALT (SGPT) elevations (≥ 3 times the upper limit of the normal range) were observed in 2.0% (8/424) of patients exposed to Remeron in a pool of short-term US controlled trials, compared to 0.3% (1/328) of placebo patients and 2.0% (3/181) of amitriptyline patients. Most of these patients with ALT increases did not develop signs or symptoms associated with compromised liver function. While some patients were discontinued for the ALT increases, in other cases, the enzyme levels returned to normal despite continued REMERON[™] (mirtazapine) treatment. Mirtazapine should be used with caution in patients with impaired hepatic function (see Pharmacokinetics section of Clinical Pharmacology, and Dosage and Administration).

Activation of Mania/Hypomania

Mania/hypomania occurred in approximately 0.2% (3/1,299 patients) of REMERON[™] (mirtazapine) treated patients in U.S.

studies. Although the incidence of mania/hypomania was very low during treatment with mirtazapine, it should be used carefully in patients with a history of mania/hypomania.

Seizures

In pre-marketing clinical trials only one seizure was reported among the 2,796 U.S. and non-U.S. patients treated with REMERON™ (mirtazapine). However, no controlled studies have been carried out in patients with a history of seizures. Therefore, care should be exercised when mirtazapine is used in these patients.

Suicide

Suicidal ideation is inherent in depression and may persist until significant remission occurs. As with any patient receiving antidepressants, high-risk patients should be closely supervised during initial drug therapy. Prescriptions of REMERON™ (mirtazapine) should be written for the smallest quantity consistent with good patient management, in order to reduce the risk of overdose.

Use in patients with concomitant illness

[We have modified the statements regarding orthostatic hypotension, in keeping with the earlier modifications regarding the statement on dizziness. We have also modified the paragraph regarding patients with renal or hepatic impairment.]

Clinical experience with REMERON™ (mirtazapine) 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.

Mirtazapine 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. Mirtazapine was not associated with clinically significant ECG abnormalities in U.S. and non-U.S. placebo controlled trials. Mirtazapine was associated with significant orthostatic hypotension in early clinical pharmacology trials. While postural blood pressure changes were not noted in later clinical trials, dizziness was observed in these trials, and was likely a manifestation of the same pathophysiological process. Consequently, caution is recommended in treating

patients who are vulnerable to changes in blood pressure (see Dizziness above).

Mirtazapine clearance is decreased in patients with moderate [glomerular filtration rate (GFR) = 11-39 mL/min/1.73 m²] and severe [GFR < 10 mL/min/1.73 m²] renal impairment, and also in patients with hepatic impairment (See Pharmacokinetic Subsection of CLINICAL PHARMACOLOGY). Caution is indicated in administering REMERON™ to such patients (see DOSAGE AND ADMINISTRATION).

Information for patients

[We have made several modifications to this section:

- We have strengthened the statement regarding psychomotor impairment given the significant occurrence of somnolence in association with the use of Remeron.
- We have slightly modified the alcohol statement.
- Given the potential seriousness of agranulocytosis, should it occur, we have added a statement advising physicians to warn patients of this risk.]

Physicians are advised to discuss the following issues with patients for whom they prescribe REMERON™:

Agranulocytosis

Patients who are to receive REMERON™ (mirtazapine) should be warned about the risk of developing agranulocytosis. Patients should be advised to report immediately the appearance of lethargy, weakness, fever, sore throat, malaise, mucous membrane ulceration or other possible signs of infection. Particular attention should be paid to any flu-like complaints or other symptoms that might suggest infection.

Interference with Cognitive and Motor Performance

REMERON™ (mirtazapine) may impair judgement, thinking, and, particularly, motor skills, because of its prominent sedative effect. The drowsiness associated with mirtazapine use may impair a patient's ability to drive, use machines or perform tasks that require alertness. Thus, patients should be cautioned about engaging in hazardous activities until they are reasonably certain that Remeron therapy does not adversely affect their ability to engage in such activities.

Completing Course of Therapy

While patients may notice improvement with REMERON™ (mirtazapine) therapy in 1 to 4 weeks, they should be advised to continue therapy as directed.

Concomitant medication

Patients should be advised to inform their physician if they are taking, or intend to take, any prescription or over-the-counter drugs since there is a potential for REMERON™ (mirtazapine) to interact with other drugs.

Alcohol

The impairment of cognitive and motor skills produced by REMERON™ (mirtazapine) has been shown to be additive with those produced by alcohol. Accordingly, patients should be advised to avoid alcohol while taking mirtazapine.

Pregnancy

Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during REMERON™ (mirtazapine) therapy.

Nursing

Patients should be advised to notify their physician if they are breast-feeding an infant.

Laboratory tests

There are no routine laboratory tests recommended.

Drug Interactions

[We have made substantial changes to this subsection, particularly in the paragraph regarding P450 enzymes. We ask that you submit the data pertinent to the inhibitory potential of mirtazapine, i.e., a more complete report on the data presented at the 10-16-95 PDAC meeting. Once we have had an opportunity to review these data, they may serve as a basis for a more definitive statement regarding this issue.]

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).

Drugs Affecting Hepatic Metabolism

The metabolism and pharmacokinetics of REMERON™ (mirtazapine) may be affected by the induction or inhibition of drug-metabolizing enzymes.

Drugs that are Metabolized by and/or Inhibit Cytochrome P450 Enzymes

Many drugs are metabolized by and/or inhibit various cytochrome P450 enzymes, e.g., 2D6, 1A2, 3A4, etc. Preliminary in vitro studies have shown that REMERON™ (mirtazapine) is a substrate for several of these enzymes, including primarily 2D6 and 1A2, and to a much lesser extent, 2C9 and 3A4. It is not known, however, whether or not mirtazapine is a substantial inhibitor of any of these enzymes. Concomitant use of mirtazapine with most other drugs metabolized by cytochrome P450 enzymes has not been formally studied. Therefore, coadministration of mirtazapine with other drugs that are metabolized by these enzymes should be considered with care.

Alcohol

Concomitant administration of alcohol (equivalent to 60 g) had a minimal effect on plasma levels of REMERON™ (15 mg) in 6 healthy male subjects. However, the impairment of cognitive and motor skills produced by REMERON™ were shown to be additive with those produced by alcohol. Accordingly, patients should be advised to avoid alcohol while taking REMERON™.

Diazepam

Concomitant administration of diazepam (15 mg) had a minimal effect on plasma levels of mirtazapine (15 mg) in 12 healthy subjects. However, the impairment of motor skills produced by REMERON™ has been shown to be additive with those caused by diazepam. Accordingly, patients should be advised to avoid diazepam and other similar drugs while taking REMERON™.

Carcinogenesis, Mutagenesis, Impairment of Fertility

[We have made several modifications in this subsection. Exposure is expressed in mg/m² rather than mg/kg. We have provided a more detailed description of the tumors observed in the mouse and rat studies. While we agree that the mechanism for tumor increase is likely non-genotoxic, we feel a more circumspect statement regarding mechanism is appropriate. Finally, we have noted that the mouse study may not have been adequate from the standpoint of MTD.]

Carcinogenicity studies were conducted with REMERON™ (mirtazapine) given in the diet at doses of 2, 20, and 200 mg/kg/day to mice and 2, 20, and 60 mg/kg/day to rats. The highest doses used are approximately 20 and 12 times the maximum recommended human dose (MRHD) of 45 mg/day on a mg/m² basis in mice and rats, respectively. There was an increased incidence of hepatocellular adenoma and carcinoma in male mice at the high dose. In rats, there was an increase in hepatocellular adenoma in females at the mid and high doses and in hepatocellular tumors and thyroid follicular adenoma/cystadenoma and carcinoma in males at the high dose. The data suggest that the above effects could possibly be mediated by non-genotoxic mechanisms, the relevance of which to humans is not known.

The doses used in the mouse study may not have been high enough to fully characterize the carcinogenic potential of REMERON™.

Mutagenesis

[We have slightly modified the mutagenicity statement.]

REMERON™ was not mutagenic in the following: an Ames test and an in vitro assay in Chinese hamster V 79 cells. It was not clastogenic in an in vitro sister chromatid exchange assay in cultured rabbit lymphocytes or in an in vivo rat micronucleus test. It was not genotoxic in an in vitro unscheduled DNA synthesis assay in HeLa cells.

Impairment of Fertility

[We have rewritten the fertility statement.]

In a fertility study in rats, Remeron™ was given at doses up to 20 times the maximum recommended human dose (MRHD) on a

mg/m² basis. Mating and conception were not affected by the drug, but estrous cycling was disrupted at doses that were 3 or more times the MRHD and pre-implantation losses occurred at 20 times the MRHD.

Pregnancy

[We have changed the pregnancy category to C based on increases in pup mortality and decreases in pup birth weights. See Approvable letter.]

Teratogenic Effects - Pregnancy Category C

Reproduction studies in pregnant rats and rabbits at doses up to 20 and 17 times the maximum recommended human dose (MRHD) on a mg/m² basis, respectively, have revealed no evidence of teratogenic effects. However, in rats, there was an increase in post-implantation losses in dams treated with Remeron[™] (mirtazapine). There was an increase in pup deaths during the first 3 days of lactation and a decrease in pup birth weights. The cause of these deaths is not known. These effects occurred at doses that were 20 times the MRHD, but not at 3 times the MRHD, on a mg/m² basis. There are no adequate and well controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers

It is not known whether mirtazapine is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when REMERON[™] (mirtazapine) Tablets are administered to nursing women.

Pediatric Use

Safety and effectiveness in children have not been established. —

Geriatric Use

[We modified this statement to reflect the actual exposure in this age group.]

Approximately 190 elderly individuals (≥ 65 years of age) participated in clinical studies with Remeron. No unusual adverse age-related phenomena were identified in this group.

Pharmacokinetic studies revealed a decreased clearance in the elderly. Caution is indicated in administering Remeron to elderly patients (see Clinical Pharmacology and Dosage and Administration).

ADVERSE REACTIONS

Associated with discontinuation of treatment

[We modified this subsection by focusing on different study pools than those in your proposed labeling and by including data for the placebo group.]

Approximately 28 percent of the 1299 patients who received Remeron in US premarketing clinical trials discontinued treatment due to an adverse experience. For short-term US placebo controlled trial, the most common events ($\geq 1\%$) associated with discontinuation and considered to be drug related (i.e., those events associated with dropout at a rate at least twice that of placebo) included:

Common Adverse Events Associated with Discontinuation of Treatment in 6-Week US Remeron Trials		
Adverse Event	Percentage of Patients Discontinuing with Adverse Event	
	Remeron (n=453)	Placebo (n=361)
Somnolence	10.4%	2.2%
Nausea	1.5%	0%

Commonly Observed Adverse Events in US Controlled Clinical Trials

[We modified this subsection by providing incidence data for both Remeron and placebo.]

The most commonly observed adverse events associated with the use of REMERON™ (incidence of 5% or greater) and not observed at an equivalent incidence among placebo-treated patients (Remeron incidence at least twice that for placebo) were:

Common Treatment-Emergent Adverse Events Associated with the Use of Remeron in 6-Week US Trials		
Adverse Event	Percentage of Patients Reporting Adverse Event	
	Remeron (n=453)	Placebo (n=361)
Somnolence	54%	18%
Increased Appetite	17%	2%
Weight Gain	12%	2%
Dizziness	7%	3%

Adverse Events Occurring at an Incidence of 1% or More Among REMERON™ Treated Patients

[We modified slightly the first paragraph in the introduction to the table that follows. In addition, we ask that you make several modifications to Table 2:

-The purpose of the table that follows is to illustrate the adverse events profile of Remeron in comparison to placebo, not in comparison to other active drugs. The latter comparison is more difficult and raises questions about the adequacy of the trials for such a comparison. Consequently, we ask that you delete the amitriptyline and trazodone columns from this table.

-Please delete the incidence data for body systems. These data are difficult to interpret and of little clinical use.

-Please delete the N's from the incidence cells; percentage by itself provides sufficient information, since the overall N's are provided above.

-Please round the percentages to the nearest integer.

-Please remove to a footnote those adverse events for which the incidence on placebo is as great as, or greater than, the incidence on Remeron.

-Within each body system category, please order the adverse events on the basis of incidence.

-Hemic and Lymphatic System should be deleted if there are no events occurring at an incidence of at least 1% for Remeron.]

-Similarly, the miscellaneous category should be deleted.

The table that follows enumerates adverse events that occurred at an incidence of 1% or more, and were more frequent than in the placebo group, among Remeron-treated patients who

participated in seven, 6-week, placebo-controlled US studies in which patients were dosed with Remeron in a range of 5-35 mg/day. This table shows the percentage of patients in each group who had at least one episode of an event at some time during their treatment. Reported adverse events were classified using a standard COSTART-based dictionary terminology.

The prescriber should be aware that these figures cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those which prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other investigations involving different treatments, uses and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and non-drug factors to the side effect incidence rate in the population studied.

TABLE 2
INCIDENCE OF ADVERSE CLINICAL EXPERIENCES (≥1%)
IN SHORT-TERM U.S. CONTROLLED STUDIES

Body System Adverse Clinical Experience	Org 3770 (N=453)	Placebo (N=361)	Amitriptyline (N=193)	Trazodone (N=49)
Body as a Whole	117 (25.8%)	98 (27.1%)	58 (30.1%)	25 (51.0%)
Asthenia	34 (7.5%)	17 (4.7%)	21 (10.9%)	6 (12.2%)
Infection	6 (1.3%)	8 (2.2%)	2 (1.0%)	2 (4.1%)
Pain	6 (1.3%)	6 (1.7%)	1 (0.5%)	2 (4.1%)
Flu Syndrome	22 (4.9%)	9 (2.5%)	8 (4.1%)	5 (10.2%)
Headache	50 (11.0%)	57 (15.8%)	30 (15.5%)	10 (20.4%)
Chest Pain	5 (1.1%)	4 (1.1%)	1 (0.5%)	2 (4.1%)
Back Pain	9 (2.0%)	3 (0.8%)	1 (0.5%)	3 (6.1%)
Cardiovascular System	26 (5.7%)	24 (6.6%)	32 (16.6%)	14 (28.6%)
Palpitation	9 (2.0%)	8 (2.2%)	7 (3.6%)	6 (12.2%)
Tachycardia	5 (1.1%)	4 (1.1%)	11 (5.7%)	6 (12.2%)
Postural Hypotension	5 (1.1%)	2 (0.6%)	10 (5.2%)	1 (2.0%)
Digestive System	207 (45.7%)	108 (29.9%)	165 (85.5%)	35 (71.4%)
Increased Appetite	76 (16.8%)	7 (1.9%)	12 (6.2%)	3 (6.1%)
Dyspepsia	13 (2.9%)	9 (2.5%)	40 (20.7%)	6 (12.2%)
Flatulence	6 (1.3%)	4 (1.1%)	3 (1.6%)	5 (10.2%)
Nausea	19 (4.2%)	19 (5.3%)	9 (4.7%)	7 (14.3%)
Dry Mouth	112 (24.7%)	54 (15.0%)	156 (80.8%)	30 (61.2%)
Constipation	57 (12.6%)	24 (6.6%)	50 (25.9%)	12 (24.5%)
Diarrhea	11 (2.4%)	16 (4.4%)	3 (1.6%)	7 (14.3%)

TABLE 2
INCIDENCE OF ADVERSE CLINICAL EXPERIENCES (≥1%)
IN SHORT-TERM U.S. CONTROLLED STUDIES

Body System Adverse Clinical Experience	Org 3770 (N=453)	Placebo (N=361)	Amitriptyline (N=193)	Trazodone (N=49)
Hemic and Lymphatic System	5 (1.1%)	2 (0.6%)	0	0
Metabolic and Nutritional Disorders	71 (15.7%)	13 (3.6%)	16 (8.3%)	8 (16.3%)
Edema	6 (1.3%)	1 (0.3%)	3 (1.6%)	2 (4.1%)
Peripheral Edema	11 (2.4%)	4 (1.1%)	2 (1.0%)	1 (2.0%)
Weight Gain	54 (11.9%)	6 (1.7%)	13 (6.7%)	2 (4.1%)
Musculoskeletal System	15 (3.3%)	11 (3.0%)	6 (3.1%)	6 (12.2%)
Myalgia	9 (2.0%)	3 (0.8%)	4 (2.1%)	0
Nervous System	288 (63.6%)	117 (32.4%)	154 (79.8%)	36 (73.5%)
Libido Decreased	6 (1.3%)	4 (1.1%)	6 (3.1%)	2 (4.1%)
Confusion	9 (2.0%)	1 (0.3%)	12 (6.2%)	2 (4.1%)
Dizziness	33 (7.3%)	12 (3.3%)	27 (14.0%)	13 (26.5%)
Abnormal Dreams	19 (4.2%)	5 (1.4%)	3 (1.6%)	3 (6.1%)
Hypertonia	6 (1.3%)	4 (1.1%)	0	1 (2.0%)
Insomnia	17 (3.8%)	21 (5.8%)	2 (1.0%)	0
Nervousness	20 (4.4%)	15 (4.2%)	20 (10.4%)	9 (18.4%)
Somnolence	243 (53.6%)	65 (18.0%)	115 (59.6%)	27 (55.1%)
Thinking Abnormal	15 (3.3%)	4 (1.1%)	8 (4.1%)	4 (8.2%)
Tremor	7 (1.5%)	2 (0.6%)	22 (11.4%)	3 (6.1%)
Respiratory System	26 (5.7%)	21 (5.8%)	14 (7.3%)	10 (20.4%)
Dyspnea	5 (1.1%)	1 (0.3%)	3 (1.6%)	2 (4.1%)
Rhinitis	6 (1.3%)	5 (1.4%)	4 (2.1%)	5 (10.2%)
Pharyngitis	8 (1.8%)	6 (1.7%)	5 (2.6%)	2 (4.1%)
Skin and Appendages	18 (4.0%)	23 (6.4%)	18 (9.3%)	6 (12.2%)
Sweating	5 (1.1%)	3 (0.8%)	6 (3.1%)	0
Special Senses	33 (7.3%)	22 (6.1%)	49 (25.4%)	19 (38.8%)
Amblyopia	11 (2.4%)	6 (1.7%)	29 (15.0%)	5 (10.2%)
Tinnitus	6 (1.3%)	3 (0.8%)	4 (2.1%)	1 (2.0%)
Taste Perversion	6 (1.3%)	3 (0.8%)	14 (7.3%)	3 (6.1%)
Urogenital System	25 (5.5%)	19 (5.3%)	23 (11.9%)	6 (12.2%)
Urinary Frequency	8 (1.8%)	5 (1.4%)	1 (0.5%)	2 (4.1%)
Miscellaneous	4 (0.9%)	8 (2.2%)	3 (1.6%)	1 (2.0%)

[We have deleted the statement regarding adverse events in the non-US database, since these data are not interpretable as presented and the statement is confusing. We feel the US data adequately characterize the adverse event profile for Remeron.]

[We have deleted the subsection on dose dependency and

adaptation. There is insufficient data upon which to base a conclusion regarding whether or not there is dose dependency. Regarding adaptation, we also feel there is insufficient data upon which to conclude that adaptation occurs.]

[We have deleted the subsection on anticholinergic syndrome. This is not a well defined concept. From the previous table, clinicians can assess for themselves the extent to which symptoms of relevance to this concept occur for Remeron relative to placebo.]

ECG Changes

In an analysis of ECGs obtained in U.S. placebo-controlled clinical trials, REMERON™ and placebo-treated patients had a similar incidence of abnormal changes from baseline at 6-8 weeks of approximately 3%. The abnormalities were generally not considered clinically significant.

Other Adverse Events Observed During the Premarketing Evaluation of REMERON™

[We have made several modifications in the introductory comments for this subsection. In addition, we have deleted several terms from the list, for various reasons, including:

- (1) nausea, vomiting, and diarrhea, since these appear in the 1% table;
- (2) immune system disorder, vascular disorder, electrocardiogram abnormality, coronary artery disorder, cardiovascular disorder, cerebrovascular disorder, tooth disorder, gastrointestinal disorder, rectal disorder, stools abnormal, thyroid disorder, erythrocyte abnormality, electrolyte abnormality, joint disorder, bone disorder, speech disorder, personality disorder, CNS stimulation, sleep disorder, paralysis, respiratory disorder, voice alteration, nasal disorder, lung disorder, pleural disorder, skin disorder, hair disorder, eye disorder, abnormal vision, ear disorder, menstrual disorder, urination impaired, penis disorder, testis disorder, kidney function abnormal, urinary tract disorder, urine abnormality, prostatic disorder, allergic reaction, cyst, arrhythmia, and hemorrhage, since these terms are too vague or general to be informative; and
- (3) neoplasm, intentional overdose, carcinoma, hernia, vascular anomaly, periodontal abscess, gingivitis, tooth discoloration, bone neoplasm, furunculosis, fibrocystic

breast, pallor, and varicose vein, since these events seem unlikely to be drug related.]

-For those terms deleted because they are too vague or general, we ask that you replace them with more informative terms, if possible.

In addition, we ask that you consider using a different rule for including nonserious events in this list. We suggest that such events be included only if reported by at least 2 patients. If you adopt this rule, please modify the introductory comments to reflect this change.]

During its premarketing assessment, multiple doses of REMERON™ (mirtazapine) were administered to 2796 patients in clinical studies. The conditions and duration of exposure to mirtazapine varied greatly, and included (in overlapping categories) open and double-blind studies, uncontrolled and controlled studies, inpatient and outpatient studies, fixed dose and titration studies. Untoward events associated with this exposure were recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of untoward events into a smaller number of standardized event categories.

In the tabulations that follow, reported adverse events were classified using a standard COSTART-based dictionary terminology. The frequencies presented, therefore, represent the proportion of the 2796 patients exposed to multiple doses of Remeron who experienced an event of the type cited on at least one occasion while receiving Remeron. All reported events are included except those already listed in the previous table, those adverse experiences subsumed under COSTART terms that are either overly general or excessively specific so as to be uninformative, and those events for which a drug cause was very remote.

It is important to emphasize that, although the events reported occurred during treatment with Remeron, they were not necessarily caused by it.

Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse events are those occurring on one or more occasions in at least 1/100 patients; infrequent adverse events are those occurring in 1/100 to 1/1000 patients; rare events are those occurring in fewer than 1/1000

patients. Only those events not already listed in Table 2 appear in this listing. Events of major clinical importance are also described in the WARNINGS and PRECAUTIONS sections.

Body as a whole: frequent: malaise, abdominal pain, abdominal syndrome acute; infrequent: chills, fever, face edema, ulcer, photosensitivity reaction, neck rigidity, neck pain, abdomen enlarged; rare: cellulitis, chest pain substernal.

Cardiovascular System: frequent: hypertension, vasodilatation; infrequent: angina pectoris, myocardial infarction, bradycardia, ventricular extrasystoles, syncope, migraine, hypotension; rare: atrial arrhythmia, bigeminy, vascular headache, pulmonary embolus, cerebral ischemia, cardiomegaly, phlebitis, left heart failure.

Digestive System: frequent: vomiting, anorexia; infrequent: eructation, glossitis, cholecystitis, nausea and vomiting, gum hemorrhage, stomatitis, colitis, liver function tests abnormal; rare: tongue discoloration, ulcerative stomatitis, salivary gland enlargement, increased salivation, intestinal obstruction, pancreatitis, aphthous stomatitis, cirrhosis of liver, gastritis, gastroenteritis, oral moniliasis, tongue edema.

Endocrine System: rare: goiter, hypothyroidism.

Hemic and Lymphatic System: rare: lymphadenopathy, leukopenia, petechia, anemia, thrombocytopenia, lymphocytosis, pancytopenia.

Metabolic and Nutritional Disorders: frequent: thirst; infrequent: dehydration, weight loss; rare: gout, SGOT increased, healing abnormal, acid phosphatase increased, SGPT increased, diabetes mellitus.

Musculoskeletal System: frequent: myasthenia, arthralgia; infrequent: arthritis, tenosynovitis; rare: pathological fracture, osteoporosis fracture, bone pain, myositis, tendon rupture, arthrosis, bursitis.

Nervous System: frequent: hypesthesia, apathy, depression, hypokinesia, vertigo, twitching, agitation, anxiety, amnesia, hyperkinesia, paresthesia; infrequent: ataxia, delirium, delusions, depersonalization, dyskinesia, extrapyramidal syndrome, libido increased, coordination abnormal, dysarthria, hallucinations, manic reaction, neurosis, dystonia, hostility, reflexes increased, emotional lability, euphoria, paranoid

reaction; rare: aphasia, nystagmus, akathisia, stupor, dementia, diplopia, drug dependence, paralysis, grand mal convulsion, hypotonia, myoclonus, psychotic depression, withdrawal syndrome.

Respiratory System: frequent: cough increased, sinusitis; infrequent: epistaxis, bronchitis, asthma, pneumonia; rare: asphyxia, laryngitis, pneumothorax, hiccup.

Skin and Appendages: frequent: pruritus, rash; infrequent: acne, exfoliative dermatitis, dry skin, herpes simplex, alopecia; rare: urticaria, herpes zoster, skin hypertrophy, seborrhea, skin ulcer.

Special Senses: infrequent: eye pain, abnormality of accommodation, conjunctivitis, deafness, keratoconjunctivitis, lacrimation disorder, glaucoma, hyperacusis, ear pain; rare: blepharitis, partial transitory deafness, otitis media, taste loss, parosmia.

Urogenital System: frequent: urinary tract infection; infrequent: kidney calculus, cystitis, dysuria, urinary incontinence, urinary retention, vaginitis, hematuria, breast pain, amenorrhea, dysmenorrhea, leukorrhea, impotence. rare: polyuria, urethritis, metrorrhagia, menorrhagia, abnormal ejaculation, breast engorgement, breast enlargement, urinary urgency.

[We have deleted the subsections entitled Laboratory Values, Hematology, Liver Function, and Cholesterol/Triglycerides since they are redundant. The important information pertinent to the parameters of interest has already been included in early sections under either Warnings or Precautions.]

DRUG ABUSE AND DEPENDENCE

[No changes have been made in this section.]

Controlled Substance Class

REMERON™ (mirtazapine) Tablets are not a controlled substance.

Physical and Psychologic Dependence

REMERON™ (mirtazapine) has not been systematically studied in animals or humans for its potential for abuse, tolerance or

physical dependence. While the clinical trials did not reveal any tendency for any drug-seeking behavior, these observations were not systematic and it is not possible to predict on the basis of this limited experience the extent to which a CNS-active drug will be misused, diverted and/or abused once marketed. Consequently, patients should be evaluated carefully for history of drug abuse, and such patients should be observed closely for signs of mirtazapine misuse or abuse (e.g., development of tolerance, incrementations of dose, drug-seeking behavior).

OVERDOSAGE

[We have revised the Human Experience paragraph to provide more data on the extent of the experience and the usual profile of signs and symptoms associated with overdose.]

Human Experience

There is very limited experience with REMERON™ (mirtazapine) overdose. In premarketing clinical studies, there were nine reports of mirtazapine overdose alone or in combination with other pharmacological agents. The only drug overdose death reported while taking REMERON™ (mirtazapine) Tablets was in combination with amitriptyline and chlorprohixene in a non-U.S. clinical study. Based on plasma levels, the REMERON™ dose taken was 30-45 mg, while plasma levels of amitriptyline and chlorprohixene were found to be at toxic levels. All other premarketing overdose cases resulted in full recovery. Signs and symptoms reported in association with overdose included disorientation, drowsiness, impaired memory, and tachycardia. There were no reports of ECG abnormalities, coma or convulsions following overdose with REMERON™ alone.

Overdose Management

Treatment should consist of those general measures employed in the management of overdose with any antidepressant. There are no specific antidotes for REMERON™. If the patient is unconscious, establish and maintain an airway to ensure adequate oxygenation and ventilation. Gastric evacuation either by the induction of emesis or lavage or both should be considered. Activated charcoal should also be considered in treatment of overdose. Cardiac and vital signs monitoring is recommended along with general symptomatic and supportive measures.

In managing overdose, consider the possibility of multiple-drug involvement. The physician should consider contacting a poison control center for additional information on the treatment of any overdose.

DOSAGE AND ADMINISTRATION

[We have made several changes to this section, including the addition of a subsection on switching patients to or from a MAOI. We have deleted the statement regarding children; the lack of data pertinent to children has already been addressed in the pediatric statement under Precautions.]

Initial Treatment

The recommended starting dose for REMERON™ (mirtazapine) is 15 mg/day, administered in a single dose, preferably in the evening prior to sleep. In the controlled clinical trials establishing the antidepressant efficacy of Remeron, the effective dose range was generally 15-45 mg/day. While the relationship between dose and antidepressant response for REMERON™ has not been adequately explored, patients not responding to the initial 15 mg dose may benefit from dose increases up to a maximum of 45 mg/day. REMERON™ has an elimination half-life of approximately 20-40 hours, therefore, dose changes should not be made at intervals of less than one to two weeks in order to allow sufficient time for evaluation of the therapeutic response to a given dose.

Elderly and Patients with Renal or Hepatic Impairment

In elderly patients, in patients with moderate to severe renal impairment, and in patients with hepatic impairment, REMERON's™ clearance is reduced by about 30%, and a dose of 30 mg should not be exceeded in these patients. (See Pharmacokinetics Subsection of CLINICAL PHARMACOLOGY).

Maintenance/Extended Treatment

There is no body of evidence available from controlled trials to indicate how long the depressed patient should be treated with Remeron. It is generally agreed, however, that pharmacological treatment for acute episodes of depression should continue for up to six months or longer. Whether the dose of antidepressant needed to induce remission is identical to the dose needed to maintain euthymia is unknown.

Switching Patients to or from a Monoamine Oxidase Inhibitor

At least 14 days should elapse between discontinuation of an MAOI and initiation of therapy with REMERON™. In addition, at least 14 days should be allowed after stopping REMERON™ before starting an MAOI.

HOW SUPPLIED

[We have made minor modifications to this section.]

REMERON™ (mirtazapine) Tablets are supplied as:

15 mg Tablets - oval, scored, yellow, coated, with "Organon" embossed on one side and "TZ3" on the other side.

Bottles of 30	NDC# 0052-0105-30
Bottles of 100	NDC# 0052-0105-91
Bottles of 500	NDC# 0052-0105-95
Unit Dose, Box of 100	NDC# 0052-0105-90*

30 mg Tablets - oval, scored, red-brown, coated, with "Organon" embossed on one side and "TZ5" on the other side.

Bottles of 30	NDC# 0052-0107-30
Bottles of 100	NDC# 0052-0107-91
Bottles of 500	NDC# 0052-0107-95
Unit Dose, Box of 100	NDC# 0052-0107-90

*Unit dose packs are provided as a blisterpack with 10 strips, each of which contain 10 tablets.

Store at controlled Room Temperature
20°-25°C (68° - 77°F) [See USP]

Dispense in a tight, light resistant container.

Caution: Federal law prohibits dispensing without prescription.

Doc LABMRTDP.AE3

Temple
mirtazapine

**Memorandum Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research**

DATE: January 8, 1996

FROM: Paul Leber, M.D.
Director,
Division of Neuropharmacological Drug Products
HFD-120

SUBJECT: Remeron (mirtazapine) NDA 20-415

TO: File NDA 20-415
 &
 Robert Temple, M.D.
 Director, Office of New Drug Evaluation 1

This memorandum briefly summarizes the basis for my endorsement of the recommendation by the Division's Review Team that Organon's NDA 20-415 for Remeron be declared approvable.

The evidence and analyses that serve as the basis of my endorsement derive from the work of the Division's review team. I have considered, too, advice given by the agency's outside expert advisors at the 10/16/95 meeting of the PDAC.

Effectiveness in Use:

Reviews and/or memoranda submitted to the administrative file by our consultant statistician, Joy D. Mele, (10/18/95) the clinical reviewer, Dr. John Balian, and the Team Leader, Dr. Laughren, (12/4/95) document that the NDA provides reports of 5 adequate and well controlled clinical investigations that show that Remeron is, within the meaning of the Act, effective in use as an antidepressant under the conditions of use recommended in the draft labeling developed by the review team.

That is not to say that the evidence developed is as extensive as we might prefer; notably, the design of the clinical trials providing positive evidence of mirtazapine's effectiveness allows investigators to titrate patients to their apparent best dose and, therefore, does not (cannot) provide information about the relationship between administered dose and clinical response.

The evidence also indicates that mirtazapine, like other antidepressant drug

products developed over the last decade, does not induce (i.e., at least under the conditions of use realized in the sponsor's controlled trials) as robust an antidepressant response as amitriptyline, the standard agent used as a control in all but one¹ of the active control studies in the sponsor's development program. Although this fact does not affect the fundamental regulatory decision regarding mirtazapine effectiveness in use (because the Act does not require that all marketed drug products within a therapeutic class be equivalent in therapeutic strength), it is, in light of the unexpectedly high incidence of agranulocytosis associated with mirtazapine use, a finding that must affect how Remeron is labeled for use (see discussion below).

Both Dr. Laughren and Ms. Mele devote some part of their discussion to 5 of the sponsor's adequate and well controlled clinical investigations that failed to find an effect of mirtazapine. Among these, Study 003-021 is most important because it had 'assay sensitivity' (detected a significant effect of amitriptyline) and, therefore, its failure to detect an effect of mirtazapine cannot be attributed to a weakness of its design or execution. However, failed and negative trials are not uncommon in commercial antidepressant drug development. Accordingly, I am not concerned that 50% of the adequate and well controlled effectiveness trials failed to provide support for Remeron's effectiveness; it's par for the course. Why this occurs remains a matter of speculation, but it seems likely to be attributable to the combined result of the interplay of wide variation in the course of depressive illness among subjects, the modest therapeutic effects of antidepressants and the uncertainties caused by treatment dependent and informative censoring processes.

The sponsor's development program, once again, provides an example of a fixed graded dose design (003-008) that failed, because of dose related censoring rates, to confirm the product's effectiveness. Although the trial's design required patients to be brought to their maximum assigned doses gradually, the procedure was evidently not successful because at trial's end there were far too few subjects in the high dose group to allow a meaningful between group comparison. Interesting, nevertheless, is the fact that the

¹ Study 003-023 employed a 3 arm design and used trazodone as an active control. The study failed to document an effect of mirtazapine as well. However, as Dr. Mille points out, the failure to find an effect of trazodone is not sufficient to dismiss the study as 'failed,' because the dose of trazodone employed was too low

few patients who were randomized to and able to tolerate the highest dose (60 mg/d), did experience the largest improvement from baseline among any of the groups studied. (see page 39 of Mele's review).

In sum, although the development program was not without its weaknesses, the sponsor has provided more than sufficient evidence to support a claim for Remeron's effectiveness in the treatment of depression.

Safety in Use

A conclusion that a drug product is "safe for use" does not imply that a product is free of risk, only that 1) the kinds of risks associated with its use, 2) the incidences at which these risks occur, and 3) the upper limit of the likely incidence of serious/catastrophic risks not observed during its clinical testing, are, taken together, judged insufficient to outweigh the benefits likely to accrue to a representative patient administered the product under the condition's of use recommended in labeling.

Although risk-benefit assessments turn on empirical findings, they are also strongly affected by the private heuristic that those rendering them use to combine and weight the knowledge, theory, sentiment and opinion that are their basis.

Accordingly, there is invariably opportunity for disagreement, if not controversy, among informed and responsible experts in regard to the relative risks and benefits of any "effective" drug product.

Remeron is a case in point. Although unquestionably effective by regulatory standards, its commercial development has been associated with the occurrence of 3 cases of agranulocytosis/ severe neutropenia (absolute neutrophil count $\leq 500/\text{mm}^3$) among approximately 2800 exposures. This corresponds to a crude rate of 1.1/1000.

This number of cases is unexpected given the estimated incidence (circa 1/10,000) of agranulocytosis in the general population which, as far as is known, is unaffected by the presence of symptomatic depression and/or depressive illness. The observed incidence of agranulocytosis is also high in comparison to that observed among patients treated in the course of clinical testing of more recently approved ADs (e.g., SSRI's); knowledge of the incidence among patients treated with older, tricyclic antidepressants, is not reliably known, but seems unlikely to be as high as that observed in the

Remeron development program. On the other hand, post-marketing experience in the Netherlands is somewhat reassuring; we are informed that no cases have so-far been reported after some 6000+ exposures. To be fair, however, case ascertainment in voluntary reporting systems is likely to be less than 100%.

In any case, whatever one's presumptions, it seems prudent to base any decision on the assumption that agranulocytosis will occur in 1/1000 patients treated with Remeron and that some fraction of these patients will die² no matter what preventative or remedial actions are taken.

Our task is to decide whether or not this risk is compatible with the approval of Remeron, and, if so, under what labeling.

The fact that Remeron causes agranulocytosis is, in my judgment, an insufficient basis to bar its approval. Marketed drug products, some with risks of agranulocytosis that exceed that seen with Remeron, are currently marketed.

The issue, in my view, therefore, is not whether Remeron can be marketed, but the labeling conditions under which it can reasonably be deemed 'safe for use.'

The most conservative position would be to repeat the stance taken with Clozapine: that is, to agree to the marketing of Remeron, but only under labeling limiting its use to patients with a history of repeated failures to respond to and/or intolerance of, other antidepressants, and then, only under some 'no blood, no drug.' testing program.

Such a combined approach seems far too severe given the information in hand. The precedent provided by the action taken with clozapine is stale. First, it

² Although all patients with mirtazapine associated agranulocytosis/severe neutropenia recovered, this does not provide a reliable basis to gauge the risk of death associated with mirtazapine induced agranulocytosis. Case fatality rates are likely to be influenced by a number of factors, including, not only the type of damage to the marrow that is caused by the drug, but the latency between development of the neutropenia and its detection, whether or not infection is present at the time of detection, the nature of the infection (anatomical site, severity, susceptibility to antibiotics, etc.).

reflected a very different set of facts; at the time our estimate was that clozapine had a cumulative annual risk of agranulocytosis exceeding 1.5% and an historical case fatality rate that had been reported to be as high as 50%. Secondly, it occurred under a very different regulatory epoch, was proposed by the drug's sponsor, and was endorsed by the PDAC.

On the other hand, it seems imprudent to market Remeron without calling prominent attention to this potentially fatal risk of use.

Accordingly, we discussed the conditions of Remeron's recommended use with our independent expert advisors at the October 1995 PDAC meeting. There is always a risk in attempting to summarize the general conclusions of complex discussions, but I believe it fair to say that our advisors were adamantly opposed to restricting the conditions under which Remeron would be recommended for use. In particular, they went on record against the tactic of recommending Remeron for use as a 'second line' treatment.

The advisors also expressed their preference for a non-restrictive approach where product labeling was concerned. In particular, they recommended that labeling not recommend any specific set of monitoring procedures.

It seems likely that the Committee's views were influenced by the testimony given by both Drs Louis Weintraub (FDA guest) and _____ (the firm's consultant) who were present as expert hematologic consultants. Each of these prominent hematologists argued that a recommendation to perform periodic monitoring would be cost-ineffective in light of the incidence of agranulocytosis expected.

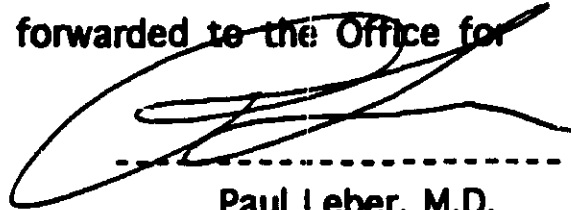
The problem, as noted in my opening remarks to this section, is that option deemed best is largely a matter of personal preference. My personal preference is not to restrict the population for whom Remeron is recommended, but to be certain that labeling adequately warns prescribers and patients about the observed incidence of agranulocytosis and the risk of fatality associated with it. I share Dr. Laughren's view that these steps will be sufficient, provided the firm's promotional activities do not undermine the thrust of our labeling, to ensure that Remeron is used appropriately within the medical community.

As to the matter of whether or not labeling should recommend a specific strategy for monitoring white counts, I am ambivalent. One option might be to enumerate the pros and cons, but make no specific recommendation; but

given the fact that this is an approvable action, I prefer to await the firm's response to see how best to resolve this matter.

Recommendation:

Issue the approvable action letter being forwarded to the Office for signature.

A handwritten signature in black ink, appearing to be 'Paul Leber', written over a horizontal dashed line.

Paul Leber, M.D.
January 8, 1996

Temple

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 4, 1995

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

SUBJECT: Recommendation for Approvable Action for Remeron
(mirtazapine) for depression

TO: File NDA 20-415
[Note: This overview should be filed with the 1-26-95
original submission.]

1.0 ADMINISTRATIVE BACKGROUND

Mirtazapine is being proposed for use in the treatment of depression.

The original IND for this compound (IND , for azomianserin as it was then known) was submitted in May, 1979 and inactivated in June, 1982. The compound was then resubmitted 7/22/82 under IND

The development of this product proceeded in subsequent years, with the most notable finding being a number of cases of neutropenia, resulting in the requirement for frequent WBC monitoring during the conduct of ph 2-3 clinical trials.

Without the benefit of a preNDA meeting, the original NDA 20-415 for Remeron was submitted 4-29-94. The NDA was voluntarily withdrawn after it became apparent that certain critical clinical data were omitted. A preNDA meeting was held with the sponsor on 7-22-94, and the NDA was re-submitted 1-26-95.

Remeron was the subject of a 10-16-95 meeting of the PDAC, and the Committee voted in favor of both its efficacy (8-0) and safety (8-0).

2.0 CHEMISTRY

Mirtazapine is a tetracyclic compound. It is a racemic mixture, and presumably both enantiomers are pharmacologically active. 15 and 30 mg tablets are proposed, in a dose range of 15-45 mg/day.

Of interest, it is structurally similar to mianserin, an antidepressant widely marketed in Europe and elsewhere.

The drug substance and product are being produced at 2 sites, i.e., in the Netherlands and in New Jersey. The Netherlands site has been inspected, and is acceptable. The New Jersey site was recently inspected for another product, and the requirement for inspection has been waived.

There are no outstanding chemistry issues at this time.

3.0 PHARMACOLOGY

Mirtazapine's pharmacological actions can be characterized predominantly as an antagonist at α -2 adrenergic, 5-HT₂, and 5-HT₁ receptors. The sponsor has suggested that the enantiomers have slightly different activities, i.e., the (+) enantiomer is an antagonist at α -2 and 5-HT₂ receptors, and the (-) enantiomer is a 5-HT₁ antagonist. However, it is also a potent antihistamine, which may explain its prominent sedative effect, and an α -1 antagonist, which may explain the prominence of orthostatic hypotension in phase 1 studies and the reporting of dizziness in phase 2-3 studies.

At the time of preparing this memo, the pharmacology review has not been signed off at a supervisory level. My preliminary impression is that mirtazapine has been adequately tested regarding reproduction toxicity and mutagenic potential, and that it does not adversely affect reproductive function, and is neither teratogenic nor mutagenic. Lifetime carcinogenicity studies were done in mice and rats. Apparently, the only statistically significant findings were: (1) an increased incidence of liver tumors in HDM mice, and (2) an increased incidence of thyroid follicular cell adenomas/cystadenomas and carcinomas in HDM rats. The sponsor proposed that the mouse liver finding is the result of an epigenetic (nongenotoxic) mechanism, and that the rat thyroid finding is the result of hepatic microsomal enzyme induction. They argued that neither finding is extrapolatable to humans.

Mirtazapine was considered at an 11-16-95 meeting of the CAC and it is my impression (report not available yet) that the only concern was whether or not the MTD had been used in the mouse carcinogenicity study. This concern would not preclude approval of this product, but would impact on whether or not there would be a phase 4 requirement for an additional carcinogenicity study. This issue is not yet resolved at the time of preparation of this memo, nor has the pharmacology group proposed language for labeling.

4.0 BIOPHARMACEUTICS

Mirtazapine is well absorbed after oral administration, concentration peaks at about 2 hours, and it has an absolute bioavailability of approximately 50%. There is only a minimal effect of food on absorption. Mirtazapine has linear pharmacokinetics over a dose range of 15-80 mg/day, and has an elimination half life of 20-40 hours across age and gender groups (females of all ages clear mirtazapine less efficiently than males). Mirtazapine is a racemic mixture (both enantiomers are active). The (-) enantiomer has a half life twice that of the (+) enantiomer, and so, is present at plasma levels approximately three times those of the (+) enantiomer. Desmethyilmirtazapine is the only pharmacologically active metabolite, but quantitatively, is not important. Mirtazapine is approximately 85% protein bound. The clearance of mirtazapine is diminished in patients with renal impairment, hepatic impairment, and in the elderly.

Two in vivo pharmacokinetic interaction studies with mirtazapine have been done (diazepam and ethanol), none suggesting any significant pharmacokinetic interactions (additive sedative effects were seen with both diazepam and ethanol). A preliminary in vitro study has demonstrated that mirtazapine is a substrate for 4 P450 isozymes: primarily 2D6 and 1A2, and to a lesser extent, 2C9 and 3A4. Preliminary in vitro inhibition studies have suggested mirtazapine has such a weak inhibitory effect at 1A2, 2D6, and 3A4 that it is unlikely to have any clinically important potential for interaction with drugs metabolized by these isozymes. Nevertheless, we will request in the approvable letter more definitive studies to address the issue of P450 metabolism and inhibition.

Cytochrome P450

5.0 CLINICAL DATA

5.1 Efficacy Data

5.1.1 Overview of Studies Pertinent to Efficacy

There were a total of 44 phase 2-3 studies pertinent to the antidepressant efficacy of mirtazapine, including 32 controlled trials and 12 uncontrolled trials. Of the controlled trials, 9 were long-term and 23 were short-term. 9 of the short-term studies were active controlled trials finding no between group differences, and these were not further reviewed. The remaining 14 trials were placebo controlled, however, 3 of these were negative but also too small to be considered adequate and well controlled, and these were not further reviewed. One of the remaining 11 studies (84008) was a study of the separate enantiomers of mirtazapine, and I will not further comment on this study since it is the racemic mixture that is proposed for marketing. The remaining 10 placebo controlled

short-term studies were the focus of our review, and I will comment on these trials under the sections to follow.

Of the 9 long-term studies, 3 were active controlled trials showing no between group differences, and these were not further reviewed. The remaining 6 trials did have placebo control groups, however, the randomization was violated and, consequently, these results were considered only descriptively.

5.1.1.1 Design Features of Pertinent 10 Short-Term Studies

These were randomized, double-blind, parallel group, 6-week studies (with the exception of 85027, which was 5 weeks) in adult outpatients (with the exception of 84023 which was an inpatient study) meeting DSMIII criteria for major depressive disorder (8 US studies) or who had a diagnosis of major depressive episode (Newcastle Endogenous/Reactive Depression Rating Scale) (2 foreign studies). One of these studies involved elderly depressed patients (study 003-023; mean age approximately 62). All 8 US studies had a 1 week placebo lead-in. All 10 included weekly visits, with baseline and weekly assessments on HAMD-21, MADRS, and the CGI (8 US studies) or Global Assessment Score (GAS) (2 foreign studies). Nine of these were titration studies in which patients were titrated in a range of 5-35 mg/day for mirtazapine in the US studies, 15-50 mg/day for study 84023, and 20-60 mg/day in study 85027. In the US studies, the dose range was 40-280 mg/day for amitriptyline and also 40-280 mg/day for trazodone (1 study).

2-Way Comparisons (Mirtazapine vs Placebo)-Titration

Two US studies and two foreign studies were of this design:

US	003-002
	003-003
Foreign	84023 (This was an inpatient study.)
	85027 (This was a 5-week study.)

3-Way Comparisons (Mirtazapine, Active Control, Placebo)-Titration

Five US studies were of this design:

003-020
003-021
003-022
003-023 (This study was in elderly depressed patients.)
003-024

Amitriptyline was the active control for all but 023, for which the active control was trazodone.

Fixed Dose Comparison Trial

There was one fixed dose study, US 003-008, which compared 4 fixed doses of mirtazapine (5, 15, 30, and 60 mg/day) with placebo.

5.1.1.2 Conduct of Pertinent Studies

Demographics and Baseline Illness Characteristics

See Table 1 in Appendix.

Groups were generally comparable on these variables, and any differences did not appear to influence study outcomes.

Patient Disposition

See Table 2 in Appendix.

Overall, dropouts were substantial in this group of studies. Differences in dropout rate did not appear to provide an explanation for differences in study outcome.

Dosing in Titration Studies

See Table 3 in Appendix.

For the positive studies, the range of mean mirtazapine doses for 6-week completers was 21-32 mg/day.

5.1.1.3 Efficacy Results

Comment on Division's Approach to Efficacy Data

Our focus was on the following 4 variables: HAMD-21 total score; HAMD-21 Item 1; MADRS total score; CGI severity (or GAS, for 2 foreign studies). We focused on analyses of change from baseline for these variables in intent to treat samples, including both observed cases analyses at each of the 6 visits of these studies and also last observation carried forward analyses at the 6 week visit. Both Wilcoxon Rank Sum Test and one-way analyses of variance were conducted. In my comments to follow, I will focus on the results for the Wilcoxon analyses, since the results were similar for the separate analyses. All p-values used in constructing the significance tables were 2-sided.

Efficacy Results for Positive Studies

In the Tables 4-8 (Appendix), I have provided a summary of the 2-sided significance levels (both LOCF and OC) for the 5 studies that I consider positive. In Table 9 (Appendix), I have provided a summary of the size of the treatment effect, using a definition of difference between drug and placebo in change from baseline for

HAMD-21 total score at week 6 (LOCF), for the 5 studies I consider positive. In Table 10 (Appendix), I have provided data on the mean change from baseline in HAMD-21 at the 6-week endpoint, both LOCF and OC, for mirtazapine and placebo, for all 10 studies.

I have not provided the detailed results for the remaining 5 trials, which I consider negative. However, I will provide comments on these studies in a later section.

5.1.2 Comment on Positive Studies

5.1.2.1 Study 003-002

Mirtazapine was consistently superior to placebo in this study, except for the week 5 and 6 OC analyses. Ms. Mele attributes this loss of significance to substantial dropouts after week 4, but argues that for both dropouts and completers, mirtazapine patients did better than placebo patients, and thus she concludes that, in the aggregate, the data provided evidence for the antidepressant effectiveness of mirtazapine. I agree.

5.1.2.2 Study 85027

Mirtazapine was consistently superior to placebo in this study on HAMD-21 Item 1 and on the MADRS total, for both LOCF and OC analyses. While the results did not achieve significance at a 0.05 level for HAMD-21 and the GAS, they were close, especially for the GAS. This study is marginal but close enough, in my view, to consider it in the positive column.

5.1.2.3 Study 003-020

Both mirtazapine and amitriptyline were superior to placebo in this study, in both OC and LOCF analyses.

5.1.2.4 Study 003-022

This was an unusual study compared to other studies in this development in several respects. Patients appeared to be quite sick at baseline, their rate of retention in the trial was quite high, and the mirtazapine dose was higher than the typical dose in these trials. The pattern of dropouts for lack of efficacy was also more typical in this trial than in some of the other trials of what one expects to see for an antidepressant. The results for this study consistently favored both mirtazapine and amitriptyline over placebo, for both LOCF and OC analyses, and thus, this is another positive study for mirtazapine.

5.1.2.5 Study 003-024

As was seen in other studies, there was an unusually high rate of dropout for lack of efficacy for mirtazapine (20%) in this study; this rate compared to 8% for amitriptyline and 32% for placebo. Nevertheless, the results favored both active drugs over placebo, for both LOCF and OC analyses, on most variables, and I consider this another positive study for mirtazapine.

5.1.3 Comment on Negative Studies

5.1.3.1 Study 003-003

One unusual finding for this study was a higher rate of dropout for lack of efficacy among mirtazapine patients (16%) compared to placebo patients (11%). There were virtually no statistically significant findings for this study, and I have not provided any of the p-values. There is no ready explanation for these negative findings.

5.1.3.2 Study 003-021

An unusual finding for this study was a very high rate of dropout for lack of efficacy for mirtazapine (26%), compared to 26% for placebo and 0% for amitriptyline. Although there were scattered positive findings favoring mirtazapine over placebo in this study, on balance mirtazapine did not fare well in comparison to placebo, while amitriptyline consistently beat placebo, at least in the LOCF analyses. Thus, this is a negative study for mirtazapine and positive study for the active control.

5.1.3.3 Study 003-023

As noted earlier, this was a study in elderly depressed patients and the active control was trazodone rather than amitriptyline. However, the mean age was approximately 62, and only a minority of patients met the usual criterion of > 65. Although there were some findings suggestive of a mirtazapine effect in this trial, in particular mirtazapine was favored over placebo in both LOCF and OC analyses for HAM-D-21 at some time points, the findings at other time points and for other variables were not consistently positive. The data for trazodone were even less convincing, perhaps having to do with the relatively low dose used (mean overall dose of only 151; mean dose for completers to 6 weeks of 220). The mirtazapine dose appeared quite adequate compared to doses used in other trials (mean dose in completers of 29). In any case, this must be considered a negative study for mirtazapine, and the interpretation for trazodone is complicated by the possibility of underdosing.

5.1.3.4 Study 003-008

There were substantial dropouts in this study, many for lack of efficacy, and there were no consistent findings favoring mirtazapine at any of the doses used over placebo. There is no ready explanation of this negative result, and this must be considered another negative study.

5.1.3.5 Study 84023

This was the only inpatient study in the development program, however, the baseline HAM-D-21 scores (26) are somewhat on the low side for depressed inpatients. The mean mirtazapine dose (33) was higher for this study than most of the outpatient studies. There were again an unusual number of dropouts for lack of efficacy (20% for mirtazapine and 28% for placebo). Indeed, the 37% dropout rate for mirtazapine is somewhat higher than expected for an inpatient depression study. The results do not favor mirtazapine over placebo, and this again must be considered a negative study for this drug. Of particular note, there were 2 completed suicides in the mirtazapine group.

5.1.4 Comment on Important Clinical Issues Regarding Mirtazapine

5.1.4.1 Evidence Bearing on the Question of Dose/Response for Efficacy

There was only one fixed dose study in this development program (003-008), and that study failed to distinguish any of the mirtazapine doses from placebo. The 4 positive US studies all involved titration of mirtazapine in a dose range of 5-35 mg/day. Consequently, if this drug is approved, the most that can be recommended in labeling would be titration within this dose range.

5.1.4.2 Clinical Predictors of Response

As part of her meta-analysis of the 7 US titration studies, Ms. Mele looked at subgroups based on age and gender. She discovered no differences in efficacy based on such groupings.

5.1.4.3 Size of Treatment Effect

Size of Treatment Effect in 5 Positive Studies			
Study Number	Mirtazapine ¹	Placebo ²	Difference ³
003-002	-11.7	-5.4	6.3
85027 ⁴	-13.4	-10.9	3.5
003-020	-10.3	-4.8	5.5
003-022	-16.1	-9.0	7.1
003-024	-12.1	-7.7	4.4

1 Mean change from baseline for mrtaz on HAMD-21 at 6wk

2 Mean change from baseline for plcbo on HAMD-21 at 6wk

3 Difference between mrtaz and plcbo

4 5-week data are presented for this study

Effect size as measured above ranged from 3.5 to 7.1 HAMD units, and these values are comparable to those observed for other recently approved antidepressant drugs.

5.1.4.4 Duration of Treatment

Ms. Mele has provided a descriptive summary of HAMD-17 data for patients extended from 6 of the US titration studies beyond the 6-week endpoint of the acute phase. While these data are suggestive of a continuation of the antidepressant response, the randomization was violated (only responders at 6 weeks were continued) and no conclusions can be drawn regarding long-term efficacy on the basis of these data. There are no other data from this development program pertinent to the question of long-term efficacy.

5.1.5 Conclusions Regarding Efficacy Data

In summary, I consider 5 of the 10 adequate and well-controlled trials to provide evidence of short-term antidepressant efficacy for mirtazapine. The evidence supporting efficacy are not overwhelming, but I believe they are sufficient to support an approvable action. However, there are several deficiencies in this program: (1) inadequate data to address dose/response for antidepressant efficacy [Note: The one fixed dose study was negative.]; (2) inadequate data to address long-term antidepressant efficacy; (3) inadequate data to address antidepressant efficacy in patients with severe, endogenous depression [Note: The one inpatient study was negative.]; and (4) no data to address antidepressant efficacy in children. We will ask the sponsor to address these deficiencies in Phase 4, and in the meantime, the labeling will acknowledge these shortcomings.

5.2 Safety Data

Clinical Data Sources for Safety Review

The safety data for mirtazapine, including the original submission, a 7-28-95 safety update, and the numerous amendments in response to our requests for additional information, were reviewed by Dr. Balian (review dated 10-19-95). This original review was based on an integrated database comprising studies completed prior to 12/93, for which no more data will be forthcoming, and on any additional serious events reported from a completed European study (86017) and from 5 ongoing studies (cutoff date of approximately 7/95).

3146 human subjects were exposed to mirtazapine in the sponsor's development program (in the integrated database available with the original submission, including 350 in phase 1 studies and 2796 in phase 2-3 studies. As noted above, serious events were provided for approximately 100 additional mirtazapine-exposed patient not yet included in the integrated database. Patients in phase 2-3 studies were roughly 65% female, predominantly white, and predominantly middle-aged. There were 190 patients over age 65. Approximately 65% of mirtazapine-treated patients in these phase 2-3 studies received modal mirtazapine doses in a range of 9-45 mg/day, with 25% getting modal mirtazapine doses > 45 mg/day. Approximately 85% of exposures were for 6 months or less, nevertheless, 377 patients received mirtazapine for at least 6 months.

In the integrated database, there were approximately 672 patient exposure years for mirtazapine, compared to 71 for placebo and 195 for active controls.

Mirtazapine has been available in the Netherlands since September, 1994. An estimated 6500 patients have been exposed to mirtazapine in the Netherlands, and we have 14 postmarketing reports, none serious, from this exposure.

Deaths

There were 12 deaths among mirtazapine-treated patients overall, including 11 in the integrated database for which the denominator and full exposure data were available. Nine of the 12 deaths were suicides, not an unusual or unexpected finding for this population (more about this later). Two other deaths were from MIs, and one from complications of cholecystitis. None of the deaths could be reasonably attributed to mirtazapine.

Adverse Dropouts

The common and drug-related adverse events leading to dropout (using a rule of a rate of $\geq 1\%$ and at least twice the placebo rate) for mirtazapine included only two: somnolence (10.4%) and

nausea (1.5%). There were 3 dropouts for severe neutropenia ($< 500/\text{mm}^3$). Otherwise, there were no serious adverse events associated with dropout in mirtazapine-exposed patients at an unexpected or disproportionate rate.

Serious Events Search

A search for serious events, using FDA's definition, identified 118 mirtazapine-treated patients having serious events among the 2796 patients in the phase 2-3 studies (65 US and 53 non-US). Of particular interest were the 3 cases on severe neutropenia noted above and discussed further below.

Suicidality Searches

A search for suicidality did not suggest any differential risk of suicidality associated with mirtazapine use.

Other Safety Findings

Common/Drug-Related AEs: The common and drug-related adverse event profile for mirtazapine included the following: increased appetite, weight gain, dizziness, and somnolence.

LAB: Potentially important and likely drug-related changes were noted in three areas, i.e., neutropenia, transaminase increases, and increases in serum cholesterol and triglycerides. (These findings are described later). Otherwise, there were no findings of clinical importance.

VS:

-One clearly drug related change associated with mirtazapine use was weight gain (discussed later).

-Orthostatic hypotension was seen during phase 1 studies, and although this problem was not apparent during ph 2-3 trials, dizziness was observed at an excess rate for mirtazapine vs placebo (7% vs 3%) during ph 2-3 trials. It is likely that the dizziness was a manifestation of the same pharmacological mechanism as that underlying the orthostasis in phase 1 studies.

-While there were a variety of other important cardiovascular events that occurred among mirtazapine exposed patients during phase 2-3 trials, there was no pattern of findings clearly suggestive of any causal linkage to mirtazapine use.

ECG: In placebo controlled trials, there was evidence of statistically significant increases in both heart rate (about 3 bpm) and QTc (about 4 msec) for mirtazapine compared to placebo, but these changes were far less than the changes seen for the amitriptyline active control group and of unlikely clinical significance.

Withdrawal Phenomena/Abuse Potential: Patients were interviewed for detection of withdrawal symptoms after premature termination or completion of short-term studies. In addition, treatment groups were compared regarding spontaneous reports following premature termination or completion of events that might be considered withdrawal phenomena. In both cases, event rates were higher for placebo than mirtazapine patients. There were also no instances suggestive of mirtazapine abuse or dependence.

Human Reproductive Data: There were 5 pregnant women exposed to mirtazapine during the development program. The outcomes of these pregnancies were not suggestive of any particular teratogenic risk associated with mirtazapine, but obviously, this experience is too limited to be a basis for any definitive statement.

Overdose Experience: The overdose experience with mirtazapine consisted of 9 reports of overdose among patients in the development program and 3 reports of overdose from postmarketing data (Netherlands). One of these overdoses was fatal, but this case involved co-administration of amitriptyline, chlorprothixene, and mirtazapine. Death in this case was most reasonably attributed to amitriptyline. All other overdose cases resulted in full recovery. Signs, and symptoms reported in association with overdose included disorientation, drowsiness, impaired memory, and tachycardia.

Summary of Drug Interactions

Drug-Demographic: An exploration of adverse events for age and gender interactions was done for 13 events that occurred at an incidence of $\geq 1\%$ for mirtazapine and for which the mirtazapine incidence was at least twice the placebo incidence. These analyses did not reveal any important differences. However, there was limited power to detect any but very substantial differences. As noted earlier, decreased clearance of mirtazapine was observed in elderly compared to younger subjects.

Drug-Disease: Except for pk studies in subjects with renal or hepatic impairment, there were no systematic attempts to explore for drug/disease interactions. A decreased clearance of mirtazapine was observed for both hepatically impaired and renally impaired patients.

Drug-Drug: (see Biopharm sections)

Summary of Important Adverse Events Considered Drug-Related

Neutropenia:

The following definitions apply to the comments that follow:

-Neutropenia = absolute neutrophil count (ANC) < 1500/mm³

Mild: ANC = 1500 - 1000

Moderate: ANC = 1000 - 500

Severe: ANC < 500

-Agranulocytosis = severe neutropenia with associated signs and symptoms, e.g., fever, infection, etc.

There were 45 cases of postbaseline (i.e., it appeared for the first time on treatment) neutropenia in mirtazapine exposed patients. [Note: Ten mirtazapine exposed patients had neutropenia at baseline, but not during exposure to drug; 3 mirtazapine exposed patients had both baseline and on drug neutropenia, but in all 3 cases the postbaseline neutropenia was mild and followed by normal ANC.] This represented a crude incidence over all exposed mirtazapine patients of 1.7%, and an incidence of 0.06 when expressed in patient years of exposure (PEY). The comparative incidences of neutropenia for mirtazapine, active controls, and placebo over the entire development program population was as follows:

	Mirtazapine	Active Controls	Placebo
Crude Incidence	1.7%	0.8%	0.5%
Neutropenia/PEY	0.06	0.04	0.04

Overall, there was no apparent relationship between dose or duration of exposure and the occurrence of neutropenia among mirtazapine exposed patients. Similarly, there was no apparent association of age or gender with the occurrence of neutropenia.

The following table enumerates the 45 mirtazapine associated cases of neutropenia on the basis of outcome and severity.

Post Baseline Neutropenia Cases for Mirtazapine					
Outcome	Mild	Mod.	Sev.	Agran	Total
Resolution on Treatment	25	3	-	-	28
Noted on Last Visit	9	-	-	-	9
Discont. for Neutropenia	3	2	1	2	8
Total	37	5	1	2	45

-For 28 cases (25 mild; 3 moderate), the neutropenia resolved despite continuing treatment.

-For 9 cases (all mild), the neutropenia was noted for the first time at the last study visit. Followup was available for only 1 of these patients, and in that case the next day value was entirely normal, suggesting the possibility of the previous value being spurious.

-The remaining 8 cases were discontinued due to the neutropenia (3 mild; 2 moderate; 1 severe; and 2 cases of agranulocytosis). All 8 of these cases recovered. Additional details on the 3 most severe cases are as follows:

85003/168: 41 y/o female; d/c on day 14 with ANC of 475; ANC nadir of 320 on day 17; then recovered 7 days later, suggesting perhaps that mature cells were being affected; never any associated symptoms.

003-010/671: 41 y/o male; fever and pharyngitis during 8th week of treatment; ANC = 0 at nadir; neutropenia recovered within a week, again suggesting that process may have been affecting mature cells.

85146/224: 59 y/o female; history of Sjogrens; d/c after 9 days with fever, rash, and SOB; subsequent severe neutropenia (ANC nadir of 6) and thrombocytopenia, and course complicated by pneumonia; neutropenia resolved within 19 days of stopping mirtazapine; bone marrow relatively normal in appearance, suggesting autoimmune process with destruction of mature cells.

The crude incidence for agranulocytosis (2 cases) or severe neutropenia (1 case) in the phase 2-3 mirtazapine exposed patients was 3/2796 (roughly 1.1 per thousand patients exposed. The 95% confidence interval for this estimate is very wide, i.e., (0.000220-0.03132), or roughly 2.2/10,000 to 3.1/1000.

There were no cases of severe neutropenia or agranulocytosis among active control patients or placebo patients in the sponsor's integrated database. However, there was a case of agranulocytosis in an imipramine exposed patient in one of the ongoing studies.

There have been no postmarketing reports of neutropenia among an estimated 6500 patients exposed to mirtazapine in the Netherlands. However, we have no information on the duration of exposure of these patients, the accuracy of the estimate of exposed patients or the level of ascertainment of exposed patients.

Comment:

Both our consultant (Louis Weintraub, M.D.) and the sponsor's consultant (M.D.) agreed that it is useful to distinguish between the more commonly occurring mild and transient neutropenias from the 3 cases of severe neutropenia. These three cases for mirtazapine represent a signal of risk for this drug that we have not observed for any recently approved psychotropics, with the well-known exception of clozapine. In particular, we did not observe any cases of agranulocytosis or severe asymptomatic neutropenia among patients exposed in comparably sized premarketing databases for any of the last 5 antidepressants approved in the US (i.e., fluoxetine, sertraline, paroxetine, venlafaxine, and nefazodone). It is also significant to note that agranulocytosis is a recognized risk (although not well quantitated) for the antidepressant mianserin that is widely marketed around the world. Mirtazapine is structurally similar to mianserin, indeed, it is azomianserin.

This risk was discussed at length at the 10-16-95 meeting of the PDAC, and the committee was unanimous in concluding that this risk should not preclude the approval of this drug for depression. I agree. The issues concerning how best to address this risk in labeling were also considered by the committee. The two pertinent issues considered by the committee were (1) whether or not routine hematologic monitoring should be recommended, and (2) whether or not mirtazapine should be considered a second line drug for depression because of this risk. Drs. Weintraub, advised against the usefulness of monitoring, given the apparent low incidence of agranulocytosis and severe neutropenia, and the committee agreed. The committee was unanimous in recommending against a second line status for this drug. While I think an argument could be made for

labeling mirtazapine as a second line drug, I agree that the risk of agranulocytosis/severe neutropenia is low and cannot yet be precisely estimated. Furthermore, there is no data to support the effectiveness of mirtazapine in patients who fail to respond to other antidepressant drugs.

Nevertheless, I think mirtazapine stands apart from recently approved antidepressants with regard to hematologic risk, and I feel that a very strong warning is indicated. I have proposed a stronger warning statement than that proposed by the sponsor, including bolding, and also advice in Information for Patients to warn patients of this risk and advise them to report to their physicians early signs and symptoms of infection. I believe that, with such a prominent Warning, Remeron will in effect become a second line drug, and with this approach there is not the implied claim of effectiveness in refractory patients that might be read into a second line status.

Somnolence:

In short-term US placebo controlled trials, the incidence of reported somnolence was as follows:

Mirtazapine	243/453 (54%)
Placebo	65/361 (18%)
Amitriptyline	115/193 (60%)

In all US trials, the incidence of discontinuation for somnolence was as follows:

Mirtazapine	140/1299 (10.8%)
Placebo	9/361 (2.5%)

Several patients on mirtazapine experienced motor vehicle accidents, which in two cases were attributed to the severe somnolent effects of the drug. It is unclear whether or not significant tolerance occurs with the somnolent effects of mirtazapine. I have recommended in labeling particularly strong advice to patients regarding their assessment of the effects of mirtazapine on ability to drive, etc.

Dizziness:

As noted under VS, I consider the dizziness observed in ph 2-3 studies as a parallel phenomenon to the orthostasis observed in phase 1 studies. Clinicians will need to be cautioned about the potential risk to patients vulnerable to the effects of hypotension, thus, we have added a precaution about possible orthostatic effects of this drug.

Appetite Increase/Weight Gain:

In short-term US placebo controlled trials, the incidence of reported appetite increase was as follows:

Mirtazapine	76/453	(17%)
Placebo	7/361	(2%)
Amitriptyline	12/193	(6%)

In all US trials, the incidence of discontinuation for appetite increase was as follows:

Mirtazapine	59/1299	(4.5%)
Placebo	0/361	(0%)

In short-term US placebo controlled trials, the incidence of weight gain of $\geq 7\%$ of body weight was reported as follows:

Mirtazapine	33/440	(7.5%)
Placebo	0/353	(0%)
Amitriptyline	11/188	(5.9%)

In all US trials, the incidence of discontinuation for weight gain was as follows:

Mirtazapine	106/1299	(8.2%)
Placebo	1/361	(0.3%)

Cholesterol & Triglyceride Increases:

There were also increases in serum cholesterol and triglycerides among mirtazapine patients, likely associated with the weight increases. [Note: These data were collected in a nonfasting state in most cases.]

In short-term US placebo controlled trials, the incidence of cholesterol increases to $\geq 20\%$ above the upper limits of normal (ULN) were reported as follows:

Mirtazapine	64/424	(15%)
Placebo	24/328	(7%)
Amitriptyline	14/181	(8%)

p < 0.001 (Mirt vs Pbo)

In short-term US placebo controlled trials, observed changes from baseline in mean serum cholesterol were as follows:

Mirtazapine	+5.8 mg/dL
Placebo	-0.8 mg/dL
Amitriptyline	+4.6 mg/dL

In short-term US placebo controlled trials, the incidence of triglyceride increases to ≥ 500 ng/dL were reported as follows:

Mirtazapine	25/424 (6%)	
Placebo	9/328 (3%)	
Amitriptyline	6/181 (3%)	$p < 0.05$ (Mirt vs Pbo)

In short-term US placebo controlled trials, observed changes from baseline in mean serum triglyceride were as follows:

Mirtazapine	+21.5 mg/dL
Placebo	-3.7 mg/dL
Amitriptyline	+14.5 mg/dL

Transaminase Increases:

In short-term US placebo controlled trials, the incidence of ALT increases to $\geq 3X$ ULN were reported as follows:

Mirtazapine	8/424 (2.0%)	
Placebo	1/328 (0.3%)	
Amitriptyline	3/181 (2.0%)	$p = 0.09$ (Mirt vs Pbo)

According to the sponsor's hepatology consultant (Paul Watkins, M.D.), there were a total of 45 patients among the 2796 exposed to mirtazapine in ph 2-3 studies with ALT elevations to $\geq 3X$ ULN (i.e., 1.6%). These 45 patients were distributed on the basis of severity as follows:

3-5 X ULN	33
5-10 X ULN	8
10-20 X ULN	3
>20 X ULN	1

While several of these patients were discontinued for their ALT increases, for others, the ALT increases resolved despite continued treatment. In some of these patients, concomitant alcohol abuse appeared to be a likely causative factor. The highest elevation reported was in a 35 y/o asymptomatic male who was discontinued with an ALT of 1255 IU/L. Three days later the ALT was near normal. All other elevations were less than 500 IU/L. Only one of these 45 patients had any symptoms associated with the ALT increase, i.e., a 29 y/o male with diarrhea, fever, and nausea associated with an ALT of 506 IU/L. The ALT had returned to normal within 3 weeks of discontinuing mirtazapine. None of these patients experienced jaundice.

The reviewing medical officer recommended routine ALT monitoring, as did the consultant from HFD-180 (John Senior, M.D.). However, we have not in the past been recommending

routine transaminase monitoring for other drugs showing this pattern of generally mild and reversible transaminitis. The question of whether or not such monitoring should be recommended in labeling was raised at the PDAC meeting 10-16-95, and the committee was not in favor of including such a recommendation in labeling. I have not included a recommendation for routine monitoring of transaminases in the labeling that I have forwarded.

Seizures: There was only 1 reported seizure among 2796 patients exposed in the phase 2-3 studies (0.04%).

Mania/Hypomania: Mania/hypomania was reported in 0.2% (3/1299) US patients taking mirtazapine, compared to no placebo patients. This is comparable to what has been observed for other antidepressants.

Conclusions Regarding Safety Data

Clearly, the main safety concern for this drug is its potential for severe neutropenia/agranulocytosis. Although the risk for this event cannot be precisely defined at this point, I believe the concern can be adequately addressed with strong labeling. The other important safety findings for this drug, in particular somnolence, weight gain, cholesterol/triglyceride increases, transaminase increases, and dizziness, can also be addressed adequately in labeling. In conclusion, I do not feel that the safety profile for this drug is sufficiently troublesome to preclude its approval.

5.3 Clinical Sections of Labeling

We have substantially rewritten the clinical sections of the draft labeling that is included with the approvable letter. The explanations for the changes are provided in bracketed comments in the draft labeling.

6.0 WORLD LITERATURE

Dr. Balian reviewed the published literature for mirtazapine included in the NDA and did not discover any previously unrecognized important safety concerns for this drug. We will ask for a literature update in the approvable letter.

7.0 FOREIGN REGULATORY ACTIONS

To my knowledge, Remeron has been marketed in the Netherlands since September, 1994, and is approved but not yet marketed in Austria, Finland, and Peru. We will ask for an update on the regulatory status of Remeron in the approvable letter.

8.0 PSYCHOPHARMACOLOGICAL DRUGS ADVISORY COMMITTEE (PDAC) MEETING

A meeting of the PDAC was held on 10-16-95 to discuss the safety and efficacy of mirtazapine for the treatment of depression. As noted above, the Committee voted in favor of both its efficacy (8-0) and safety (8-0).

9.0 DSI INSPECTIONS

Of the 5 studies I consider positive for this NDA, inspections have been completed and are satisfactory for 2, i.e., Bremner (003-022) and Smith (003-024). Inspections are pending on 2 others: Walshe (003-020) and Deshay (85027). Claghorn was the principal investigator for the fifth study (003-002); he has been inspected in the recent past and has essentially passed inspection.

10.0 LABELING AND APPROVABLE LETTER

10.1 Final Draft of Labeling Attached to Approvable Package

Our proposed draft of labeling is attached to the approvable letter. As noted, we have made substantial changes to the sponsor's draft dated 1-26-95.

10.2 Foreign Labeling

We have received translated labeling for the countries in which mirtazapine is approved and provisionally approved. These documents were reviewed and considered in our modifications to the proposed labeling for this product.

10.3 Approvable Letter

The approvable letter includes draft labeling and requests for: a safety update; a literature update; a regulatory status update; a request for a relapse prevention trial; a request for a study in depressed children; a request for studies to further explore dose/response for effectiveness; additional in vitro interaction studies to further address the metabolism of this drug by P450 isozymes and also its inhibitory effects on P450 isozymes; additional information on the postmarketing experience in the Netherlands, particularly regarding the extent of exposure and the extent of ascertainment for serious hematological events.

11.0 CONCLUSIONS AND RECOMMENDATIONS

I believe that Organon has submitted sufficient data to support the conclusion that mirtazapine is effective in the treatment of depression. However, mirtazapine stands apart from the 5 most

recently approved antidepressants in that it is associated with a potential for a very serious hematological event, i.e., agranulocytosis. These 5 previously approved drugs appear not to be associated with this event or any comparably serious adverse event. Nevertheless, mirtazapine is also the first of a class of antidepressants that may act partly through α -2 antagonism to be considered for approval by FDA. Given the heterogeneity of the population of depressed patients who are the candidates for these various treatments, I believe that this drug should be considered approvable, despite its unusual risk, because of the possibility that some subgroup of this population may benefit preferentially from a drug in this class. I hold this view only because I believe that, with strong labeling, this drug can be used in a reasonably safe manner. Consequently, I recommend that we issue the attached approvable letter with our labeling proposal and the above noted requests for updates, etc., in anticipation of final approval.

cc:
Orig NDA
HFD-120
HFD-120/TLaughren/PLeiber/Balian/Mosholder
HFD-100/RTemple

DOC: MEMMRTDP.AE1

Table 1 Baseline Demographics and Illness Characteristics						
Study Number	Group	Age-yr (mean)	% Female	% White	HAMD-21 (mean)	CGI-S (mean)
003-002	MRT	39	55%	98%	24	4.3
	PBO	40	48%	89%	25	4.2
003-003	MRT	43	47%	98%	25	4.3
	PBO	43	67%	93%	26	4.3
84023	MRT	46	58%	--	26	--
	PBO	46	48%	--	26	--
85027	MRT	40	64%	--	26	--
	PBO	41	70%	--	26	--
003-020	MRT	44	46%	100%	28	4.5
	AMI	43	45%	98%	29	4.7
	PBO	45	62%	95%	30	4.8
003-021	MRT	45	56%	93%	24	4.1
	AMI	44	54%	88%	25	4.2
	PBO	48	56%	83%	24	4.0
003-022	MRT	39	59%	96%	33	5.1
	AMI	39	74%	96%	32	5.2
	PBO	37	70%	98%	31	5.1
003-023	MRT	63	43%	100%	25	3.7
	TRZ	61	60%	96%	25	4.0
	PBO	62	59%	100%	24	3.9
003-024	MRT	44	54%	98%	28	4.4
	AMI	43	51%	94%	28	4.5
	PBO	40	67%	100%	28	4.3
003-008	MRT ¹	40	66%	86%	26	4.3
	PBO	39	61%	86%	25	4.2

1 These values represent aggregate measures across all 4 dose groups for this study.

Table 2 Patient Disposition Completers to Week 6: n/N¹(%)			
Study Number	Mirtazapine	Amitriptyline	Placebo
003-002	26/44 (59%)	--	19/44 (43%)
003-003	27/45 (60%)	--	24/45 (53%)
84023	37/59 (63%)	--	30/54 (56%)
85027	51/64 (80%)	--	48/66 (73%)
003-020	23/41 (56%)	25/40 (63%)	24/39 (62%)
003-021	22/45 (49%)	27/48 (56%)	21/48 (44%)
003-022	37/49 (76%)	40/50 (80%)	36/50 (72%)
003-023	37/49 (76%)	32/48 (67%) ²	32/48 (67%)
003-024	30/50 (60%)	35/49 (71%)	27/48 (56%)

- 1 n = number completing and N = intent-to-treat sample
2 Trazodone was active control for study 003-023

Table 3 Mean Dose (mg) for Completers to Week 6 in Titration Studies			
Study Number	Mirtazapine	Amitriptyline	Trazodone
003-002	21	--	--
003-003	27	--	--
84023	33	--	--
85027	52	--	--
003-020	24	37	--
003-021	21	116	--
003-022	31	186	--
003-023	29	--	220
003-024	22	144	--

Table 4 Summary of Significance Levels ¹ (2-sided) for Pairwise Comparisons Mirtazapine vs Placebo in Study 003-002							
Key Outcome Variables	Mirtazapine vs Placebo						
	Week ²						
	1	2	3	4	5	6	
HAMD-21 Total							
LOCF							*
OC	*	*	*	*	-	-	
HAMD-21 Item 1							
LOCF							*
OC	*	*	*	*	-	-	
MADRS Total							
LOCF							*
OC	*	*	*	*	-	-	
CGI Severity							
LOCF							*
OC	*	*	*	*	-	-	

1 Based on Wilcoxon Rank Sum Analysis

* = $p \leq 0.05$

t = $p \leq 0.10$

- = $p > 0.10$

2 End of weeks 1-6

Table 5 Summary of Significance Levels ¹ (2-sided) for Pairwise Comparisons Mirtazapine vs Placebo in Study 85027						
Key Outcome Variables	Mirtazapine vs Placebo					
	Week ² 1 2 3 4 5					
HAMD-21 Total LOCF OC					-	t
HAMD-21 Item 1 LOCF OC				*	*	*
MADRS Total LOCF OC				*	*	*
Global Assessment Scale LOCF OC				t	t	t

1 Based on Wilcoxon Rank Sum Analysis

* = $p \leq 0.05$

t = $p \leq 0.10$

- = $p > 0.10$

2 End of weeks 2, 4, and 5

Table 6 Summary of Significance Levels ¹ (2-sided) for Pairwise Comparisons (Mirtazapine vs Pbo and Amitriptyline vs Pbo) in Study 003-020												
Key Outcome Variables	Mirtazapine vs Pbo						Amitriptyline vs Pbo					
	Week ² 1 2 3 4 5 6						Week 1 2 3 4 5 6					
HAMD-21 Total LOCF OC						*						*
	-	t	*	*	-	*	-	*	*	*	t	*
HAMD-21 Item 1 LOCF OC						*						*
	-	-	-	-	-	*	-	-	-	-	-	*
MADRS Total LOCF OC						*						*
	-	-	-	t	-	t	-	*	*	*	t	*
CGI Severity LOCF OC						*						*
	-	-	*	*	t	*	-	*	*	*	*	*

1 Based on Wilcoxon Rank Sum Analysis

* = $p \leq 0.05$

t = $p \leq 0.10$

- = $p > 0.10$

2 End of weeks 1-6

NDA 20415

2 OF 8

Table 7
Summary of Significance Levels¹ (2-sided) for Pairwise
Comparisons (Mirtazapine vs Pbo and Amitriptyline vs Pbo) in
Study 003-022

Key Outcome Variables	Mirtazapine vs Pbo	Amitriptyline vs Pbo
	Week ² 1 2 3 4 5 6	Week 1 2 3 4 5 6
HAMD-21 Total LOCF OC	 * * * * * *	 * * * * * *
HAMD-21 Item 1 LOCF OC	 * * * * * *	 t t * * t - -
MADRS Total LOCF OC	 * t * - - * *	 * * * * * *
CGI Severity LOCF OC	 * - t - - * *	 * - t * * * *

1 Based on Wilcoxon Rank Sum Analysis

* = $p \leq 0.05$

t = $p \leq 0.10$

- = $p > 0.10$

2 End of weeks 1-6

Table 8 Summary of Significance Levels ¹ (2-sided) for Pairwise Comparisons (Mirtazapine vs Pbo and Amitriptyline vs Pbo) in Study 003-024												
Key Outcome Variables	Mirtazapine vs Pbo						Amitriptyline vs Pbo					
	Week ² 1 2 3 4 5 6						Week 1 2 3 4 5 6					
HAMD-21 Total LOCF OC						*						*
	t	*	-	*	-	t	*	*	*	*	-	*
HAMD-21 Item 1 LOCF OC						*						*
	t	-	*	*	t	t	-	*	*	*	-	*
MADRS Total LOCF OC						*						*
	t	*	*	*	-	*	*	*	*	*	-	*
CGI Severity LOCF OC						*						*
	-	t	t	*	-	t	*	*	*	*	-	*

1 Based on Wilcoxon Rank Sum Analysis

* = $p \leq 0.05$

t = $p \leq 0.10$

- = $p > 0.10$

2 End of weeks 1-6

Table 9 Size of Treatment Effect in Positive Mirtazapine Studies [Difference Between Mirtazapine and Amitriptyline vs Placebo in Mean Change from Baseline for HAMD-21 Total at Week 6 (LOCF)]			
Study 003-002			
Groups	Baseline ¹	Baseline-Wk6 ²	Difference ³
Placebo	24.7	-5.4	
Mirtazapine	24.2	-11.7	6.3
Study 85027			
Groups	Baseline ¹	Baseline-Wk5 ²	Difference ³
Placebo	26.2	-10.9	
Mirtazapine	26.4	-13.4	3.5
Study 003-020			
Groups	Baseline ¹	Baseline-Wk6 ²	Difference ³
Placebo	29.5	-4.8	
Mirtazapine	27.8	-10.3	5.5
Amitriptyline	29.2	-11.5	6.7
Study 003-022			
Groups	Baseline ¹	Baseline-Wk6 ²	Difference ³
Placebo	31.2	-9.0	
Mirtazapine	33.0	-16.1	7.1
Amitriptyline	32.0	-14.1	5.1
Study 003-024			
Groups	Baseline ¹	Baseline-Wk6 ²	Difference ³
Placebo	27.6	-7.7	
Mirtazapine	27.5	-12.1	4.4
Amitriptyline	27.6	-13.9	6.2

1 Baseline mean HAMD-21 total score

2 Change from baseline to week 6 (LOCF)

3 Difference between mirtazapine and amitriptyline vs placebo in mean change from baseline to week 6 (LOCF) for HAMD-21

Table 10 Mean Change from Baseline in HAMD-21 at 6-week Endpoint ¹ (LOCF and OC) for Mirtazapine and Placebo (10 Studies)				
Study Number	LOCF		OC	
	Mirtazapine	Placebo	Mirtazapine	Placebo
003-002	-11.7	-5.4	-14.5	-11.4
003-003	-10.4	-8.8	-14.0	-11.5
84023	-10.9	-9.0	-14.2	-11.9
85027	-13.4	-10.9	-14.7	-11.8
003-020	-10.3	-4.8	-13.0	-6.2
003-021	-11.7	-9.5	-13.8	-17.4
003-022	-16.1	-9.0	-19.4	-11.0
003-023	-9.9	-6.6	-11.1	-7.6
003-024	-12.1	-7.7	-15.7	-11.1
003-008 ²	-8.1	-9.6	-16.6	-11.4

1 Study 85027 was a 5-week study.

2 Results are presented for the 60 mg/day group.

MEMORANDUM

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

DATE: JAN 25 1996

FROM: Director, Office of Drug Evaluation I, HFD-101

SUBJECT: Mirtazapine (NDA 20-415, Remeron)

TO: Dr. Paul Leber, HFD-120

The excellent primary and secondary reviews make the situation with Mirtazapine quite clear. The effectiveness of M is supported by 5 controlled trials, but the dose-response is unclear not-well-defined. You noted that M "like other antidepressant drug products developed over the last decade" is not as effective as amitriptyline. I don't think that conclusion is clear for most of those drugs (the SSRI's, e.g.) but it may be so in this case. In the 4 studies with placebo, M, and A, A was a little better in 2 (003-020 and 003-024) little worse in 1 (003-022), and importantly better in one (003-021), where A was significantly better than placebo and M was not. I think those results do suggest A may be better than M but that the matter is not really settled.

With respect to dose, I note that although some trials used doses of up to the 50 mg 007 vs series did not, stopping at 35 mg. Those studies were, however, as supportive as any studies conducted. The studies going to higher doses were weaker on average. I would suggest making 35 mg the top recommended dose. That may be a problem with planned 15 and 30 mg tablets, but perhaps 30 mg could be the high dose. There is evidence supporting the effectiveness of a 20 mg dose, as significant drug placebo differences in a number of trials are present by 2 weeks a time, when the dose is only 20 mg. (See studies 003-002, 003-022 and 003-021). Study 003-023, not consistently significant for most measures at all weeks, did show favorable results at week 2 on HAM-D21. The fact that the European studies (84023 and 84027) went to 50 mg (or apparently, higher) doesn't suggest value of those doses, as 84023 never showed a treatment effect and 84027 was certainly not more impressive than other trials.

The pooled 003 data (Mele, p. 53) for percent of patients with 50% or greater change on HAM-D21, or other measures (p. 54), also suggest that the treatment-placebo difference increases only a little after 2 weeks for Mirtazapine, again suggesting only a small benefit, at best, for doses beyond 20 mg.

This drug seems fairly obviously one for which work-up of individual enantiomers should have been considered, as it appears somnolence and alpha blockade, neither very good characteristics for a drug not intended to be a sedative or antihypertensive may be associated with one enantiomer.

With respect to labeling, see comments on the labeling attached to the approvable letter. A few specific points:

1. I agree with the conclusion that monitoring wbc or hepatic function in this case is not reasonable; the "get" rate is just too low. We have urged monitoring when rates of agranulocytosis get into the 1% range and when severe liver injury (including jaundice in some) is known.
2. I think the leukopenia warning deserves a box.
3. I think doses above 35 mg are not supported, although they seem to be tolerated and suggest a top recommended dose of 30 mg.

A handwritten signature in dark ink, appearing to read "Robert Temple". The signature is somewhat stylized and includes a horizontal line extending to the right.

Robert Temple, M.D.

ATTACHMENT 2

DRAFT LABELING PROPOSAL

Temp Made-up

Note: Brackets [] embedded within the text that follows include comments and explanations concerning the proposed draft labeling. For some sections, few changes were proposed, while others required extensive modification. This revision is based on the version of labeling submitted in the August 21, 1995 original submission. If you feel that further revisions are necessary to this draft, please use this exact document as the starting document. Please use the 'strikeout' font to indicate the material you wish to delete and the 'redline' font to indicate the material you wish to add.

REMERON™
(mirtazapine) Tablets

DESCRIPTION

[We have made a slight modification to the first sentence of the first paragraph in this section, since it suggested that Remeron is a unique antidepressant. Rather, we have clarified that the chemical structure is unique.]

Shouldn't this say it's a racemic mixture

REMERON™ (mirtazapine) is an antidepressant for oral administration with a tetracyclic chemical structure unrelated to selective serotonin reuptake inhibitors, tricyclics or monoamine oxidase inhibitors (MAOI). Mirtazapine belongs to the piperazino-azepine group of compounds. It is designated 1,2,3,4,10,14b-hexahydro-2-methylpyrazino [2,1-a] pyrido [2,3-c] benzazepine and has the empirical formula of C₁₇H₁₉N₃. Its molecular weight is 265.36. The structural formula is:

[Insert structural formula here.]

Mirtazapine is a white to creamy white crystalline powder which is slightly soluble in water.

REMERON™ is supplied for oral administration as scored film-coated tablets containing 15 or 30 mg of mirtazapine. Each tablet also contains corn starch, hydroxypropyl cellulose, magnesium stearate, colloidal silicon dioxide, lactose and other inactive ingredients.

CLINICAL PHARMACOLOGY

Pharmacodynamics

[We have made several modifications to this section.

-Our current approach to this subsection of antidepressant labeling is to acknowledge that the pharmacological basis for the antidepressant action of any of these drugs is not known with any certainty. Alternatively, we believe it is most informative to neutrally describe the pharmacology of mirtazapine, except in those instances when the linkage to clinical effects is adequately known, e.g., histamine antagonism for sedation and α_1 adrenergic antagonism for orthostatic effects. We have also deleted the discussion of enantiomer specific effects since the data supporting those statements are complicated; a much longer discussion would be needed to adequately address this issue, and there would be no clear clinical relevance for such a discussion.

-We have deleted the qualifier "initial" to sedative, since the somnolent effects of mirtazapine appear to persist in many patients.

-We have added a reference to the α_1 adrenergic antagonist effect, as a probable explanation for the hypotensive effects observed in phase 1 studies and dizziness observed in phase 2-3 studies.

-We have deleted the reference to anxiolytic effects, since mirtazapine has not been developed as an anxiolytic and its effects on anxiety symptoms have been addressed more appropriately in the Clinical Trials subsection.

-The references to the absence of anticholinergic side effects and cardiovascular effects have been deleted, since these issues are more appropriately addressed in the Adverse Reactions section. However, in this regard, we have noted the moderate antimuscarinic effect of Remeron.

-The reference to sleep effects has been deleted from this section, since the clinical effects on sleep disturbance in association with depression have been more appropriately addressed in the Clinical Trials subsection.]

The mechanism of action of REMERON[™] (mirtazapine), as with other antidepressants, is unknown.

② Shouldn't the different properties associated with each enantiomer be noted?

Preclinical studies have shown that mirtazapine acts as an antagonist at central presynaptic α_2 adrenergic inhibitory autoreceptors, an action which is postulated to result in an increase in central noradrenergic activity.

Mirtazapine is ^{also} a potent antagonist of 5-HT₂ and 5-HT₁ receptors.

Mirtazapine is a potent antagonist of histamine (H₁) receptors, a property that may explain the sedative effects seen in patients receiving this drug.

Mirtazapine is a moderate ^{peripheral} α_1 adrenergic antagonist, a property that may explain orthostatic hypotension and dizziness reported in association with its use.

Mirtazapine is a moderate antagonist at muscarinic receptors.

In healthy normal volunteers, a single dose of mirtazapine (15 mg) had moderate effects on subjective and objective psychometric tests designed to detect decreases in cognition, memory, attention, psychomotor performance and muscle tone.

The effects of mirtazapine and diazepam appeared to be additive.

Pharmacokinetics

[We have made numerous changes in the organization and content of this subsection.]

REMERON™ (mirtazapine) is rapidly and completely absorbed following oral administration, ~~and its absolute bioavailability is approximately 50%.~~ Peak plasma concentrations are reached within about 2 hours following an oral dose. The presence of food in the stomach has a minimal effect on both the rate and extent of absorption and does not require a dosage adjustment.

Mirtazapine is approximately 85% bound to plasma proteins over a concentration range of 0.01 to 10 $\mu\text{g/mL}$. ~~Binding appears to be reversible. The binding affinity of mirtazapine to human liver proteins is 2.8 times greater than to human plasma proteins. As with all drugs that are protein bound, care should be exercised when co-administering medications that may interact with mirtazapine at protein binding sites (see Drug Interactions under the Precautions section).~~

by CYP2D6
enzymes
and

Mirtazapine is extensively metabolized, ^{and has an absolute bioavailability of about 80%} and is ^{primarily} eliminated via urine (75%) and feces, (15%) within 96 hours. Major pathways of biotransformation are demethylation and hydroxylation followed by conjugation. Several unconjugated metabolites possess pharmacological activity but are present in the plasma at very low levels. The (-) enantiomer has an elimination half-life that is approximately twice as long ^{as the (+)} and achieves plasma levels that are three times as high as that of the (+) enantiomer.

glucuronide
15-20%
(+)
conjugation

3 This is unclear
20-40 pretty
sig. Is it
20 may (young)
40 women/d
or what?

Plasma levels are linear ^{related to dose} over a dose range of 15 to 80 mg. The mean elimination half-life of mirtazapine after oral administration ranges from approximately 20-40 hours across age and gender subgroups, with females of all ages exhibiting significantly longer elimination half-lives than males. Steady state plasma levels of mirtazapine are attained within 5 days, with ^{about 50%} minimal accumulation (accumulation ratio = 1.5).

(- vs -)

Population Subgroups

from previous p

Liver Disease - Following a single 15 mg oral dose of mirtazapine, the oral clearance of mirtazapine was decreased by approximately 30% in hepatically impaired patients compared to subjects with normal hepatic function. Caution is indicated in administering REMERON™ to patients with compromised hepatic function (see Precautions and Dosage and Administration).

Renal Disease - Following a single 15 mg oral dose of mirtazapine, patients with moderate [glomerular filtration rate (GFR) = 11-39 mL/min/1.73 m²] and severe [GFR < 10 mL/min/1.73 m²] renal impairment had reductions in mean oral clearance of mirtazapine of about 30% and 50%, respectively, compared to normal subjects. Caution is indicated in administering REMERON™ to patients with compromised renal function (see Precautions and Dosage and Administration).

was
this
clearly
attributable
to the
age
difference
or not?

Elderly Patients - Following oral administration of mirtazapine 20 mg/day for 7 days to subjects of varying ages (range, 25-74), oral clearance of mirtazapine was reduced in the elderly compared to the younger subjects. The differences were most striking in males, with a 40% lower clearance in elderly males compared to younger males, while the clearance in elderly females was only 10% lower compared to younger females. Caution is indicated in administering REMERON™ to elderly patients (see Precautions and Dosage and Administration).

Smokers - Cigarette smoking increased the mean oral clearance of mirtazapine by about 30%.

Showing
Clinical Trials Supporting the Effectiveness Claim

[Consistent with recently approved antidepressant products, we have added this subsection to describe in some detail the clinical trials supporting the effectiveness claim.]

Why not 5 studies

The efficacy of REMERON™ (mirtazapine) as a treatment for depression was established in ~~four~~ placebo-controlled, 6-week trials in adult outpatients meeting DSM-III criteria for major depression. Patients were titrated with mirtazapine ~~in~~ ^{from} a dose range of ~~5-25~~ ^{10 up to 35} mg/day. Overall, these studies demonstrated mirtazapine to be superior to placebo on at least three of the following four measures: 21-Item Hamilton Depression Rating Scale (HDRS) total score; HDRS Depressed Mood Item; CGI Severity score; and Montgomery and Asberg Depression Rating Scale (MADRS). Significant differences were also found for certain factors of the HDRS (e.g., anxiety/somatization factor and sleep disturbance factor). The mean mirtazapine dose for patients who completed these four studies ranged from 21 to 32 mg/day. *A fifth study of similar design utilized a higher dose (up to 50 mg) per day and also showed effectiveness. In these studies, effects were usually apparent by 2 weeks.* ~~Descriptive analyses on the basis of age and gender did not suggest any differential responsiveness on the basis of these subgroupings.~~

subjects of the population did not reveal

INDICATIONS AND USAGE

[We have made a number of modifications to this section:
-We have changed the language for the claim to that currently used for antidepressants.
-We have added a reference to the Clinical Pharmacology subsection for details regarding the clinical trials supporting the claim.
-While DSMIII criteria were used in the conduct of your trials, we nevertheless think it would be appropriate to use the currently accepted definition of major depression, i.e., DSMIV.
-We have deleted the statement regarding anxiety reduction, since the effect on anxiety associated with depression has been more appropriately addressed in the Clinical Trials subsection.
-We have added a statement acknowledging that mirtazapine has not been adequately studied in depressed inpatients.]

Small amount of effect with higher doses

-Finally, since we disagree that you have provided adequate data pertinent to the question of long-term efficacy, we have added a statement noting that mirtazapine has not been adequately studied with regard to long-term efficacy or relapse prevention.

REMERON™ (mirtazapine) Tablets are indicated for the treatment of depression.

The efficacy of REMERON™ in the treatment of depression was established in six week controlled trials of outpatients whose diagnoses corresponded most closely to the Diagnostic and Statistical Manual of Mental Disorders - 3rd edition (DSM-III) category of major depressive disorder (see CLINICAL PHARMACOLOGY).

A major depressive episode (DSM-IV) implies a prominent and relatively persistent (nearly every day for at least 2 weeks) depressed or dysphoric mood that usually interferes with daily functioning, and includes at least five of the following nine symptoms: depressed mood, loss of interest in usual activities, significant change in weight and/or appetite, insomnia or hypersomnia, psychomotor agitation or retardation, increased fatigue, feelings of guilt or worthlessness, slowed thinking or impaired concentration, a suicide attempt or suicidal ideation.

The antidepressant effectiveness of REMERON™ (mirtazapine) in hospitalized depressed patients has not been adequately studied.

The effectiveness of REMERON™ in long-term use, that is, for more than 6 weeks, has not been systematically evaluated in controlled trials. Therefore, the physician who elects to use REMERON™ for extended periods should periodically evaluate the long-term usefulness of the drug for the individual patient.

CONTRAINDICATIONS

REMERON™ (mirtazapine) Tablets are contraindicated in patients with a known hypersensitivity to mirtazapine.

WARNINGS

Agranulocytosis

(We believe a rate of about 0.1% agranulocytosis requires bone marrow)
[We have modified this statement by deleting the reference to the imipramine case. There are not adequate data in your database to make comparisons between mirtazapine and other antidepressants with regard to incidence of severe neutropenia and agranulocytosis. Rather, the point of this warning is to alert clinicians to the possibility of these serious events occurring in association with the use of mirtazapine. We have also added more details regarding mirtazapine to more fully describe the observed findings. Finally, we have added bold print to emphasize the importance of this signal.]

③ I believe a Bar is needed. It can be placed here, as 1st warning (Bar)
In premarketing clinical trials, two (one with Sjögren's Syndrome) out of 2,796 patients treated with REMERON™ (mirtazapine) Tablets developed agranulocytosis [absolute neutrophil count (ANC) < 500/mm³ with associated signs and symptoms, e.g., fever, infection, etc.] and a third patient developed severe neutropenia [ANC < 500/mm³ without any associated symptoms]. For these three patients, onset of severe neutropenia was detected on days 9, 17, and 61 of treatment, respectively. All three patients recovered after Remeron was stopped. These three cases yield a crude incidence of severe neutropenia (with or without associated infection) of approximately 1.1 per thousand patients exposed, with a very wide 95% confidence interval, i.e., 2.2 cases per 10,000 to 3.1 cases per 1000. If a patient develops a sore throat, fever, stomatitis or other signs of infection, along with a low WBC count, treatment with REMERON™ should be discontinued and the patient should be closely monitored. If the total WBC count is below 2000/mm³ or the ANC is below 1000/mm³, bone marrow aspiration should be considered to ascertain granulopoietic status. If granulopoiesis is determined to be deficient, appropriate cultures should be performed and an appropriate antibiotic regimen instituted.

MAO Inhibitors

[We have made a minor editorial change to this statement. In keeping with recent labeling practice regarding this warning, we have added bold print for emphasis.]

② where this came from
In patients receiving other antidepressants in combination with a monoamine oxidase inhibitor (MAOI) and in patients who

have recently discontinued an antidepressant drug and then are started on an MAOI, there have been reports of serious, and sometimes fatal, reactions. Since there are no human data pertinent to such an interaction with REMERON™, it is recommended that REMERON™ not be used in combination with an MAOI, or within 14 days of initiating or discontinuing therapy with an MAOI.

PRECAUTIONS

General

Somnolence

[We have modified this statement:

- We have added data for the control groups for comparison.
- We have added data on dropouts for somnolence.
- We have noted the occurrence of motor vehicle accidents attributed to Remeron, since this may be a measure of the severity of this adverse event in some patients.
- We don't believe that adequate data pertinent to the question of tolerance have been collected, consequently, we have simply noted that fact.]

In U.S. controlled studies, somnolence was reported in 56% of patients treated with REMERON™ (mirtazapine), compared to 18% for placebo and 60% for amitriptyline. In a pooled analysis of all premarketing US studies, somnolence resulted in discontinuation for 10.8% of Remeron treated patients, compared to 2.5% for placebo. Several patients treated with Remeron experienced motor vehicle accidents, which in two cases were attributed to the severe somnolent effects of Remeron. It is unclear whether or not tolerance develops to the somnolent effects of Remeron.

Dizziness

[We have modified this statement:

- We have added data for the control groups for comparison.
- We don't believe that adequate data pertinent to the question of tolerance have been collected, consequently, we have simply noted that fact.]
- We believe there is a link between the orthostatic hypotension observed in ph 1 studies and the dizziness observed in ph 2-3 studies that needs to be acknowledged

What kind of "reactions"

②
Don't
we usually
say some
thing here
about
machinery
& drug
(I see p4
p 12)

here. Consequently, we have noted this likely connection, and cautioned about the use of Remeron in patients likely to be vulnerable to adverse effects of lowered blood pressure.]

In U.S. controlled studies, dizziness was reported in 7% of patients treated with REMERON™ (mirtazapine), compared to 3% for placebo and 14% for amitriptyline. It is unclear whether or not tolerance develops to the dizziness observed in association with the use of Remeron. While the orthostatic hypotension observed in early clinical pharmacology trials with Remeron was not frequently observed in later clinical trials, the dizziness observed in association with mirtazapine use in these later trials was likely a manifestation of the same pharmacological basis for the orthostatic hypotension, i.e., probably α_1 antagonism. Thus, the prescriber should be aware that there is some risk of postural hypotension in association with mirtazapine use. REMERON™ 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).

Increased Appetite/Weight Gain

[[We have modified this statement:

-We have replaced the data provided in your draft of labeling with data that we feel are more pertinent, including the proportions of patients dropping out for weight gain.

-We have added data for the control groups for comparison.].

In US controlled studies, appetite increase was reported in 17% of patients treated with REMERON™ (mirtazapine), compared to 2% for placebo and 6% for amitriptyline. In these same trials, weight gain of $\geq 7\%$ of body weight was reported in 7.5% of patients treated with mirtazapine, compared to 0% for placebo and 5.9% for amitriptyline. In a pooled analysis of premarketing US studies, weight gain resulted in discontinuation for 8.2% of mirtazapine treated patients, compared to 0.3% for placebo.

Cholesterol/Triglycerides

[We have modified this statement:

-We have replaced data suggested in your proposed labeling with data we feel are more pertinent.

-We have added data for the control groups for comparison.

-We have also added definitions of what is meant by clinically significant.]

In U.S. controlled studies, nonfasting cholesterol increases to $\geq 20\%$ above the upper limits of normal were observed in 15% of patients treated with REMERON™ (mirtazapine), compared to 7% for placebo and 8% for amitriptyline. In these same studies, nonfasting triglyceride increases to ≥ 500 mg/dL were observed in 6% of patients treated with mirtazapine, compared to 3% for placebo and 3% for amitriptyline.

Transaminase Elevations

[We have slightly modified this statement.]

Clinically significant ALT (SGPT) elevations (≥ 3 times the upper limit of the normal range) were observed in 2.0% (8/424) of patients exposed to Remeron in a pool of short-term US controlled trials, compared to 0.3% (1/328) of placebo patients and 2.0% (3/181) of amitriptyline patients. Most of these patients with ALT increases did not develop signs or symptoms associated with compromised liver function. While some patients were discontinued for the ALT increases, in other cases, the enzyme levels returned to normal despite continued REMERON™ (mirtazapine) treatment. Mirtazapine should be used with caution in patients with impaired hepatic function (see Pharmacokinetics section of Clinical Pharmacology, and Dosage and Administration).

Activation of Mania/Hypomania

Mania/hypomania occurred in approximately 0.2% (3/1,299 patients) of REMERON™ (mirtazapine) treated patients in U.S. studies. Although the incidence of mania/hypomania was very low during treatment with mirtazapine, it should be used carefully in patients with a history of mania/hypomania.

Seizures

In pre-marketing clinical trials only one seizure was reported among the 2,796 U.S. and non-U.S. patients treated with REMERON™ (mirtazapine). However, no controlled studies have been carried out in patients with a history of seizures. Therefore, care should be exercised when mirtazapine is used in these patients.

Suicide

Suicidal ideation is inherent in depression and may persist until significant remission occurs. As with any patient receiving antidepressants, high-risk patients should be closely supervised during initial drug therapy. Prescriptions of REMERON™ (mirtazapine) should be written for the smallest quantity consistent with good patient management, in order to reduce the risk of overdose.

Use in patients with concomitant illness

[We have modified the statements regarding orthostatic hypotension, in keeping with the earlier modifications regarding the statement on dizziness. We have also modified the paragraph regarding patients with renal or hepatic impairment.]

Clinical experience with REMERON™ (mirtazapine) 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.

(?)
what's that
angina,
CHF?

Mirtazapine has not been systematically evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Mirtazapine was not associated with clinically significant ECG abnormalities in U.S. and non-U.S. placebo controlled trials. Mirtazapine was associated with significant orthostatic hypotension in early clinical pharmacology trials. While postural blood pressure changes were not noted in later clinical trials, dizziness was observed in these trials, and was likely a manifestation of the same pathophysiological process. Consequently, caution is recommended in treating patients who are vulnerable to changes in blood pressure (see Dizziness above).

Mirtazapine clearance is decreased in patients with moderate [glomerular filtration rate (GFR) = 11-39 mL/min/1.73 m²] and severe [GFR < 10 mL/min/1.73 m²] renal impairment, and also in patients with hepatic impairment (See Pharmacokinetic Subsection of CLINICAL PHARMACOLOGY). Caution is indicated in administering REMERON™ to such patients (see DOSAGE AND ADMINISTRATION).

Information for patients

[We have made several modifications to this section:

-We have strengthened the statement regarding psychomotor impairment given the significant occurrence of somnolence in association with the use of Remeron.

-We have slightly modified the alcohol statement.

-Given the potential seriousness of agranulocytosis, should it occur, we have added a statement advising physicians to warn patients of this risk.]

Physicians are advised to discuss the following issues with patients for whom they prescribe REMERON™:

Agranulocytosis

Patients who are to receive REMERON™ (mirtazapine) should be warned about the risk of developing agranulocytosis. Patients should be advised to report immediately the appearance of lethargy, weakness, fever, sore throat, malaise, mucous membrane ulceration or other possible signs of infection. Particular attention should be paid to any flu-like complaints or other symptoms that might suggest infection.

Interference with Cognitive and Motor Performance

REMERON™ (mirtazapine) may impair judgement, thinking, and, particularly, motor skills, because of its prominent sedative effect. The drowsiness associated with mirtazapine use may impair a patient's ability to drive, use machines or perform tasks that require alertness. Thus, patients should be cautioned about engaging in hazardous activities until they are reasonably certain that Remeron therapy does not adversely affect their ability to engage in such activities.

Completing Course of Therapy

While patients may notice improvement with REMERON™ (mirtazapine) therapy in 1 to 4 weeks, they should be advised to continue therapy as directed.

Concomitant medication

Patients should be advised to inform their physician if they are taking, or intend to take, any prescription or over-the-counter drugs since there is a potential for REMERON™ (mirtazapine) to interact with other drugs.

Alcohol

The impairment of cognitive and motor skills produced by REMERON™ (mirtazapine) has been shown to be additive with those produced by alcohol. Accordingly, patients should be advised to avoid alcohol while taking mirtazapine.

Pregnancy

Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during REMERON™ (mirtazapine) therapy.

Nursing

Patients should be advised to notify their physician if they are breast-feeding an infant.

Laboratory tests

There are no routine laboratory tests recommended.

Drug Interactions

[We have made substantial changes to this subsection, particularly in the paragraph regarding P450 enzymes. We ask that you submit the data pertinent to the inhibitory potential of mirtazapine, i.e., a more complete report on the data presented at the 10-16-95 PDAC meeting. Once we have had an opportunity to review these data, they may serve as a basis for a more definitive statement regarding this issue.]

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).

Drugs Affecting Hepatic Metabolism

The metabolism and pharmacokinetics of REMERON™ (mirtazapine) may be affected by the induction or inhibition of drug-metabolizing enzymes.

Drugs that are Metabolized by and/or Inhibit Cytochrome P450 Enzymes

Many drugs are metabolized by and/or inhibit various cytochrome P450 enzymes, e.g., 2D6, 1A2, 3A4, etc. Preliminary in vitro studies have ~~revealed~~ ^{shown} that REMERON™ (mirtazapine) is a substrate for several of these enzymes, including primarily 2D6 and 1A2, and to a much lesser extent, 2C9 and 3A4. ~~However,~~ ^{not known,} It is unknown whether or not mirtazapine is a substantial inhibitor of any of these enzymes. Concomitant use of mirtazapine with most other drugs metabolized by cytochrome P450 enzymes has not been formally studied. Therefore, coadministration of mirtazapine with other drugs that are metabolized by these enzymes should be considered with care.

Drugs Bound to Plasma Protein

Because REMERON™ (mirtazapine) is bound to plasma proteins (85%), care should be exercised when mirtazapine is co-administered to a patient who may be receiving another drug which is highly protein bound.

Alcohol

Concomitant administration of alcohol (equivalent to 60 g) had a minimal effect on plasma levels of REMERON™ (15 mg) in 6 healthy male subjects. However, the impairment of cognitive and motor skills produced by REMERON™ were shown to be additive with those produced by alcohol. Accordingly, patients should be advised to avoid alcohol while taking REMERON™.

I don't believe this low a level requires attention

Diazepam

Concomitant administration of diazepam (15 mg) had a minimal effect on plasma levels of mirtazapine (15 mg) in 12 healthy subjects. However, the impairment of motor skills produced by REMERON™ has been shown to be additive with those caused by diazepam. Accordingly, patients should be advised to avoid diazepam and other similar drugs while taking REMERON™.

Carcinogenesis, Mutagenesis, Impairment of Fertility

[We have made several modifications in this subsection. Exposure is expressed in mg/m² rather than mg/kg. We have provided a more detailed description of the tumors observed in the mouse and rat studies. While we agree that the mechanism for tumor increase is likely non-genotoxic, we feel a more circumspect statement regarding mechanism is appropriate. Finally, we have noted that the mouse study may not have been adequate from the standpoint of MTD.]

*4/25/93
S. J. H. H.*
Carcinogenicity studies were conducted with REMERON™ (mirtazapine) given in the diet at doses of 2, 20, and 200 mg/kg/day to mice and 2, 20, and 60 mg/kg/day to rats. The highest doses used are approximately 20 and 12 times the maximum recommended human dose (MRHD) of 45 mg/day on a mg/m² basis in mice and rats, respectively. [There was an increased incidence of hepatocellular adenoma and carcinoma in male mice receiving 20 times the MRHD, of hepatocellular adenoma in female rats receiving 4 or 12 times the MRHD (with a trend toward increased hepatocellular tumors in male rats receiving 12 times the MRHD), and of thyroid follicular adenoma/cystadenoma and carcinoma in male rats receiving 12 times the MRHD (with a trend toward an increase in adenoma/cystadenoma at the lower doses)]. The data suggest that the above effects could possibly be mediated by non-genotoxic mechanisms, the relevance of which to humans is not known.

5/11/93
The doses used in the mouse study may not have been high enough to adequately characterize the carcinogenic potential of REMERON™.

Mutagenesis

[We have slightly modified the mutagenicity statement.]

REMERON™ was not mutagenic in the following: an Ames test^{and} an in vitro assay in Chinese hamster V 79 cells, ~~and an in vivo~~ rat micronucleus test. It was not clastogenic in an in vitro sister chromatid exchange assay in cultured rabbit lymphocytes and it was not genotoxic in an in vitro unscheduled DNA synthesis assay in HeLa cells.

Impairment of Fertility

[We have rewritten the fertility statement.]

In a fertility study in rats, Remeron™ was given at doses up to 20 times the maximum recommended human dose (MRHD) on a mg/m² basis. Mating and conception were not affected by the drug, but estrous cycling was disrupted at doses that were 3 or more times the MRHD.

Pregnancy

[We have changed the pregnancy category to C based on increases in pup mortality and decreases in pup birth weights. See Approvable letter.]

Teratogenic Effects - Pregnancy Category C

Reproduction studies in pregnant rats and rabbits at doses up to 20 and 17 times the maximum recommended human dose (MRHD) on a mg/m² basis, respectively, have revealed no evidence of teratogenic effects. However, in rats, there was an increase in pre- and post-implementation losses in dams treated with Remeron™ (mirtazapine). There was an increase in pup deaths during the first 3 days of lactation and a decrease in pup birth weights. The cause of these deaths is not known. These effects occurred at doses that were 20 times the MRHD, but not at 3 times the MRHD, on a mg/m² basis. There are no adequate and well controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers

It is not known whether mirtazapine is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when REMERON™ (mirtazapine) Tablets are administered to nursing women.

Pediatric Use

Safety and effectiveness in children have not been established.

Geriatric Use

[We modified this statement to reflect the actual exposure in this age group.]

Approximately 190 elderly individuals (≥ 65 years of age) participated in clinical studies with Remeron. No unusual adverse age-related phenomena were identified in this ~~cohort~~^{group} of elderly patients treated with Remeron. (Pharmacokinetic studies revealed a decreased clearance in the elderly. Caution is indicated in administering Remeron to elderly patients (see Clinical Pharmacology and Dosage and Administration).

ADVERSE REACTIONS

Associated with discontinuation of treatment

[We modified this subsection by focusing on different study pools than those in your proposed labeling and by including data for the placebo group.]

Approximately 28 percent of the 1299 patients who received Remeron in US premarketing clinical trials discontinued treatment due to an adverse experience. For short-term US placebo controlled trial, the most common events ($\geq 1\%$) associated with discontinuation and considered to be drug related (i.e., those events associated with dropout at a rate at least twice that of placebo) included:

Common Adverse Events Associated with Discontinuation of Treatment in 6-Week US Remeron Trials		
Adverse Event	Percentage of Patients Discontinuing with Adverse Event	
	Remeron (n=453)	Placebo (n=361)
Somnolence	10.4%	2.2%
Nausea	1.5%	0%

Commonly Observed Adverse Events in US Controlled Clinical Trials

[We modified this subsection by providing incidence data for both Remeron and placebo.]

The most commonly observed adverse events associated with the use of REMERON™ (incidence of 5% or greater) and not observed at an equivalent incidence among placebo-treated patients (Remeron incidence at least twice that for placebo) were:

Common Treatment-Emergent Adverse Events Associated with the Use of Remeron in 6-Week US Trials		
Adverse Event	Percentage of Patients Reporting Adverse Event	
	Remeron (n=453)	Placebo (n=361)
Somnolence	54%	18%
Increased Appetite	17%	2%
Weight Gain	12%	2%
Dizziness	7%	3%

Adverse Events Occurring at an Incidence of 1% or More Among REMERON™ Treated Patients

[We modified slightly the first paragraph in the introduction to the table that follows. In addition, we ask that you make several modifications to Table 2:
 -The purpose of the table that follows is to illustrate the adverse events profile of Remeron in comparison to placebo, not in comparison to other active drugs. The latter comparison is more difficult and raises questions

about the adequacy of the trials for such a comparison. Consequently, we ask that you delete the amitriptyline and trazodone columns from this table.

-Please delete the incidence data for body systems. These data are difficult to interpret and of little clinical use.

-Please delete the N's from the incidence cells; percentage by itself provides sufficient information, since the overall N's are provided above.

-Please round the percentages to the nearest integer.

-Please remove to a footnote those adverse events for which the incidence ^{on placebo is as great as, or greater than, the incidence on} ~~is equal to or greater for placebo~~ ~~compared to Remeron.~~

-Within each body system category, please order the adverse events on the basis of incidence.

-Hemic and Lymphatic System should be deleted if there are no events occurring at an incidence of at least 1% for Remeron.]

-Similarly, the miscellaneous category should be deleted.

The table that follows enumerates adverse events that occurred at an incidence of 1% or more, and were more frequent than in the placebo group, among Remeron-treated patients who participated in seven, 6-week, placebo-controlled US studies in which patients were dosed with Remeron in a range of 5-35 mg/day. This table shows the percentage of patients in each group who had at least one episode of an event at some time during their treatment. Reported adverse events were classified using a standard COSTART-based dictionary terminology.

The prescriber should be aware that these figures cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those which prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other investigations involving different treatments, uses and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and non-drug factors to the side effect incidence rate in the population studied.

TABLE 2
INCIDENCE OF ADVERSE CLINICAL EXPERIENCES (≥1%)
IN SHORT-TERM U.S. CONTROLLED STUDIES

Body System Adverse Clinical Experience	Org 3770 (N=453)	Placebo (N=361)	Amitriptyline (N=193)	Trazodone (N=49)
Body as a Whole	117 (25.8%)	98 (27.1%)	58 (30.1%)	25 (51.0%)
Asthenia	34 (7.5%)	17 (4.7%)	21 (10.9%)	6 (12.2%)
Infection	6 (1.3%)	8 (2.2%)	2 (1.0%)	2 (4.1%)
Pain	6 (1.3%)	6 (1.7%)	1 (0.5%)	2 (4.1%)
Flu Syndrome	22 (4.9%)	9 (2.5%)	8 (4.1%)	5 (10.2%)
Headache	50 (11.0%)	57 (15.8%)	30 (15.5%)	10 (20.4%)
Chest Pain	5 (1.1%)	4 (1.1%)	1 (0.5%)	2 (4.1%)
Back Pain	9 (2.0%)	3 (0.8%)	1 (0.5%)	3 (6.1%)
Cardiovascular System	26 (5.7%)	24 (6.6%)	32 (16.6%)	14 (28.6%)
Palpitation	9 (2.0%)	8 (2.2%)	7 (3.6%)	6 (12.2%)
Tachycardia	5 (1.1%)	4 (1.1%)	11 (5.7%)	6 (12.2%)
Postural Hypotension	5 (1.1%)	2 (0.6%)	10 (5.2%)	1 (2.0%)
Digestive System	207 (45.7%)	108 (29.9%)	165 (85.5%)	35 (71.4%)
Increased Appetite	76 (16.8%)	7 (1.9%)	12 (6.2%)	3 (6.1%)
Dyspepsia	13 (2.9%)	9 (2.5%)	40 (20.7%)	6 (12.2%)
Flatulence	6 (1.3%)	4 (1.1%)	3 (1.6%)	5 (10.2%)
Nausea	19 (4.2%)	19 (5.3%)	9 (4.7%)	7 (14.3%)
Dry Mouth	112 (24.7%)	54 (15.0%)	156 (80.8%)	30 (61.2%)
Constipation	57 (12.6%)	24 (6.6%)	50 (25.9%)	12 (24.5%)
Diarrhea	11 (2.4%)	16 (4.4%)	3 (1.6%)	7 (14.3%)
Hemic and Lymphatic System	5 (1.1%)	2 (0.6%)	0	0
Metabolic and Nutritional Disorders	71 (15.7%)	13 (3.6%)	16 (8.3%)	8 (16.3%)
Edema	6 (1.3%)	1 (0.3%)	3 (1.6%)	2 (4.1%)
Peripheral Edema	11 (2.4%)	4 (1.1%)	2 (1.0%)	1 (2.0%)
Weight Gain	54 (11.9%)	6 (1.7%)	13 (6.7%)	2 (4.1%)
Musculoskeletal System	15 (3.3%)	11 (3.0%)	6 (3.1%)	6 (12.2%)
Myalgia	9 (2.0%)	3 (0.8%)	4 (2.1%)	0
Nervous System	288 (63.6%)	117 (32.4%)	154 (79.8%)	36 (73.5%)
Libido Decreased	6 (1.3%)	4 (1.1%)	6 (3.1%)	2 (4.1%)
Confusion	9 (2.0%)	1 (0.3%)	12 (6.2%)	2 (4.1%)
Dizziness	33 (7.3%)	12 (3.3%)	27 (14.0%)	13 (26.5%)
Abnormal Dreams	19 (4.2%)	5 (1.4%)	3 (1.6%)	3 (6.1%)
Hypertonia	6 (1.3%)	4 (1.1%)	0	1 (2.0%)
Insomnia	17 (3.8%)	21 (5.8%)	2 (1.0%)	0
Nervousness	20 (4.4%)	15 (4.2%)	20 (10.4%)	9 (18.4%)
Somnolence	243 (53.6%)	65 (18.0%)	115 (59.6%)	27 (55.1%)
Thinking Abnormal	15 (3.3%)	4 (1.1%)	8 (4.1%)	4 (8.2%)

Tremor	7 (1.5%)	2 (0.6%)	22 (11.4%)	3 (6.1%)
Respiratory System	26 (5.7%)	21 (5.8%)	14 (7.3%)	10 (20.4%)
Dyspnea	5 (1.1%)	1 (0.3%)	3 (1.6%)	2 (4.1%)
Rhinitis	6 (1.3%)	5 (1.4%)	4 (2.1%)	5 (10.2%)
Pharyngitis	8 (1.8%)	6 (1.7%)	5 (2.6%)	2 (4.1%)
Skin and Appendages	18 (4.0%)	23 (6.4%)	18 (9.3%)	6 (12.2%)
Sweating	5 (1.1%)	3 (0.8%)	6 (3.1%)	0
Special Senses	33 (7.3%)	22 (6.1%)	49 (25.4%)	19 (38.8%)
Amblyopia	11 (2.4%)	6 (1.7%)	29 (15.0%)	5 (10.2%)
Tinnitus	6 (1.3%)	3 (0.8%)	4 (2.1%)	1 (2.0%)
Taste Perversion	6 (1.3%)	3 (0.8%)	14 (7.3%)	3 (6.1%)
Urogenital System	25 (5.5%)	19 (5.3%)	23 (11.9%)	6 (12.2%)
Urinary Frequency	8 (1.8%)	5 (1.4%)	1 (0.5%)	2 (4.1%)
Miscellaneous	4 (0.9%)	8 (2.2%)	3 (1.6%)	1 (2.0%)

[We have deleted the statement regarding adverse events in the non-US database, since these data are not interpretable as presented and the statement is confusing. We feel the US data adequately characterize the adverse event profile for Remeron.]

[We have deleted the subsection on dose dependency and adaptation. There is insufficient data upon which to base a conclusion regarding whether or not there is dose dependency. Regarding adaptation, we also feel there is insufficient data upon which to conclude that adaptation occurs.]

[We have deleted the subsection on anticholinergic syndrome. This is not a well defined concept. From the previous table, clinicians can assess for themselves the extent to which symptoms of relevance to this concept occur for Remeron relative to placebo.]

ECG Changes

In an analysis of ECGs obtained in U.S. placebo-controlled clinical trials, REMERON™ and placebo-treated patients had a similar incidence of abnormal changes from baseline at 6-8 weeks of approximately 3%. The abnormalities were generally not considered clinically significant.

Other Adverse Events Observed During the Premarketing Evaluation of REMERON™

[We have made several modifications in the introductory comments for this subsection. In addition, we have deleted several terms from the list, for various reasons, including:

(1) nausea, vomiting, and diarrhea, since these appear in the 1st table;

(2) immune system disorder, vascular disorder, electrocardiogram abnormality, coronary artery disorder, cardiovascular disorder, cerebrovascular disorder, tooth disorder, gastrointestinal disorder, rectal disorder, stools abnormal, thyroid disorder, erythrocyte abnormality, electrolyte abnormality, joint disorder, bone disorder, speech disorder, personality disorder, CNS stimulation, sleep disorder, paralysis, respiratory disorder, voice alteration, nasal disorder, lung disorder, pleural disorder, skin disorder, hair disorder, eye disorder, abnormal vision, ear disorder, menstrual disorder, urination impaired, penis disorder, testis disorder, kidney function abnormal, urinary tract disorder, urine abnormality, and prostatic disorder, since these terms are too vague or general to be informative; and

(3) neoplasm, intentional overdose, carcinoma, hernia, vascular anomaly, periodontal abscess, gingivitis, tooth discoloration, bone neoplasm, furunculosis, and fibrocystic breast, since these events seem unlikely to be drug related.]

-For those terms deleted because they are too vague or general, we ask that you replace them with more informative terms, if possible.

In addition, we ask that you consider using a different rule for including nonserious events in this list. We suggest that such events be included only if reported by at least 2 patients. If you adopt this rule, please modify the introductory comments to reflect this change.]

During its premarketing assessment, multiple doses of REMERON™ (mirtazapine) were administered to 2796 patients in clinical studies. The conditions and duration of exposure to mirtazapine varied greatly, and included (in overlapping categories) open and double-blind studies, uncontrolled and controlled studies, inpatient and outpatient studies, fixed dose and titration studies. Untoward events associated with

See
P 23
and add
to list

this exposure were recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of untoward events into a smaller number of standardized event categories.

In the tabulations that follow, reported adverse events were classified using a standard COSTART-based dictionary terminology. The frequencies presented, therefore, represent the proportion of the 2796 patients exposed to multiple doses of Remeron who experienced an event of the type cited on at least one occasion while receiving Remeron. All reported events are included except those already listed in the previous table, those adverse experiences subsumed under COSTART terms that are either overly general or excessively specific so as to be uninformative, and those events for which a drug cause was very remote.

It is important to emphasize that, although the events reported occurred during treatment with Remeron, they were not necessarily caused by it.

Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse events are those occurring on one or more occasions in at least 1/100 patients; infrequent adverse events are those occurring in 1/100 to 1/1000 patients; rare events are those occurring in fewer than 1/1000 patients. Only those events not already listed in Table 2 appear in this listing. Events of major clinical importance are also described in the WARNINGS and PRECAUTIONS sections.

Body as a whole: frequent: malaise, abdominal pain, abdominal syndrome acute; infrequent: allergic reaction, chills, cyst fever, face edema, ulcer, photosensitivity reaction, neck rigidity, neck pain, abdomen enlarged; rare: cellulitis, chest pain substernal. *Vague*
Vague

Cardiovascular System: frequent: hypertension, vasodilatation; infrequent: angina pectoris, myocardial infarction, arrhythmia, bradycardia, ventricular extrasystoles, syncope, migraine, hypotension, rare: atrial arrhythmia, bigeminy, vascular headache, hemorrhage, pulmonary embolus, cerebral ischemia, pallor, cardiomegaly, phlebitis, left heart failure, varicose veins.

too vague
not an ADR
not an ADR
too vague (of what?)

Digestive System: frequent: vomiting, anorexia; infrequent: eructation, glossitis, cholecystitis, nausea and vomiting, gum hemorrhage, stomatitis, colitis, liver function tests abnormal; rare: tongue discoloration, ulcerative stomatitis, salivary gland enlargement, increased salivation, intestinal obstruction, pancreatitis, aphthous stomatitis, cirrhosis of liver, gastritis, gastroenteritis, oral moniliasis, tongue edema.

Endocrine System: rare: goiter, hypothyroidism.

Hemic and Lymphatic System: rare: lymphadenopathy, leukopenia, petechia, anemia, thrombocytopenia, lymphocytosis, pancytopenia.

Metabolic and Nutritional Disorders: frequent: thirst; infrequent: dehydration, weight loss; rare: gout, SGOT increased, healing abnormal, acid phosphatase increased, SGPT increased, diabetes mellitus.

Musculoskeletal System: frequent: myasthenia, arthralgia; infrequent: arthritis, tenosynovitis; rare: pathological fracture, osteoporosis fracture, bone pain, myositis, tendon rupture, arthrosis, bursitis.

Nervous System: frequent: hypesthesia, apathy, depression, hypokinesia, vertigo, twitching, agitation, anxiety, amnesia, hyperkinesia, paresthesia; infrequent: ataxia, delirium, delusions, depersonalization, dyskinesia, extrapyramidal syndrome, libido increased, coordination abnormal, dysarthria, hallucinations, manic reaction, neurosis, dystonia, hostility, reflexes increased, emotional lability, euphoria, paranoid reaction; rare: aphasia, nystagmus, akathisia, stupor, dementia, diplopia, drug dependence, paralysis, grand mal convulsion, hypotonia, myoclonus, psychotic depression, withdrawal syndrome.

Respiratory System: frequent: cough increased, sinusitis; infrequent: epistaxis, bronchitis, asthma, pneumonia; rare: asphyxia, laryngitis, pneumothorax, hiccup.

Skin and Appendages: frequent: pruritus, rash; infrequent: acne, exfoliative dermatitis, dry skin, herpes simplex, alopecia; rare: urticaria, herpes zoster, skin hypertrophy, seborrhea, skin ulcer.

Special Senses: infrequent: eye pain, abnormality of accommodation, conjunctivitis, deafness, keratoconjunctivitis, lacrimation disorder, glaucoma, hyperacusis, ear pain; rare: blepharitis, partial transitory deafness, otitis media, taste loss, parosmia.

Urogenital System: frequent: urinary tract infection; infrequent: kidney calculus, cystitis, dysuria. urinary incontinence, urinary retention, vaginitis, hematuria, breast pain, amenorrhea, dysmenorrhea, leukorrhea, impotence, rare: polyuria, urethritis, metrorrhagia, menorrhagia, abnormal ejaculation, breast engorgement, breast enlargement, urinary urgency.

[We have deleted the subsections entitled Laboratory Values, Hematology, Liver Function, and Cholesterol/Triglycerides since they are redundant. The important information pertinent to the parameters of interest has already been included in early sections under either Warnings of Precautions.]

DRUG ABUSE AND DEPENDENCE

[No changes have been made in this section.]

Controlled Substance Class

REMERON™ (mirtazapine) Tablets are not a controlled substance.

Physical and Psychologic Dependence

REMERON™ (mirtazapine) has not been systematically studied in animals or humans for its potential for abuse, tolerance or physical dependence. While the clinical trials did not reveal any tendency for any drug-seeking behavior, these observations were not systematic and it is not possible to predict on the basis of this limited experience the extent to which a CNS-active drug will be misused, diverted and/or abused once marketed. Consequently, patients should be evaluated carefully for history of drug abuse, and such patients should be observed closely for signs of mirtazapine misuse or abuse (e.g., development of tolerance, incrementations of dose, drug-seeking behavior).

OVERDOSAGE

[We have revised the Human Experience paragraph to provide more data on the extent of the experience and the usual profile of signs and symptoms associated with overdose.]

Human Experience

There is very limited experience with REMERON™ (mirtazapine) overdose. In premarketing clinical studies, there were nine reports of mirtazapine overdose alone or in combination with other pharmacological agents. The only drug overdose death reported while taking REMERON™ (mirtazapine) Tablets was in combination with amitriptyline and chlorprohixene in a non-U.S. clinical study. Based on plasma levels, the REMERON™ dose taken was 30-45 mg, while plasma levels of amitriptyline and chlorprohixene were found to be at toxic levels. All other premarketing overdose cases resulted in full recovery. Signs and symptoms reported in association with overdose included disorientation, drowsiness, impaired memory, and tachycardia. There were no reports of ECG abnormalities, coma or convulsions following overdose with REMERON™ alone.

Overdose Management

Treatment should consist of those general measures employed in the management of overdose with any antidepressant. There are no specific antidotes for REMERON™. If the patient is unconscious, establish and maintain an airway to ensure adequate oxygenation and ventilation. Gastric evacuation either by the induction of emesis or lavage or both should be considered. Activated charcoal should also be considered in treatment of overdose. Cardiac and vital signs monitoring is recommended along with general symptomatic and supportive measures.

In managing overdosage, consider the possibility of multiple-drug involvement. The physician should consider contacting a poison control center for additional information on the treatment of any overdose.

DOSAGE AND ADMINISTRATION

[We have made several changes to this section, including the addition of a subsection on switching patients to or from a MAOI. We have deleted the statement regarding children; the lack of data pertinent to children has already been addressed in the pediatric statement under Precautions.]

Initial Treatment

The recommended starting dose for REMERON™ (mirtazapine) is 15 mg/day, administered in a single dose, preferably in the evening prior to sleep. In the controlled clinical trials establishing the antidepressant efficacy of Remeron, the effective dose range was generally 15-35 mg/day. While the relationship between dose and antidepressant response for REMERON™ has not been adequately explored, patients not responding to the initial 15 mg dose may benefit from dose increases up to a maximum of 35 mg/day. REMERON™ has an elimination half-life of approximately 20-40 hours, therefore, dose changes should not be made at intervals of less than one to two weeks in order to allow sufficient time for evaluation of the therapeutic response to a given dose.

Elderly and Patients with Renal or Hepatic Impairment

In elderly patients, in patients with moderate to severe renal impairment, and in patients with hepatic impairment, REMERON™ should be dosed with care. (See Pharmacokinetics Subsection of CLINICAL PHARMACOLOGY).

Maintenance/Extended Treatment

There is no body of evidence available from controlled trials to indicate how long the depressed patient should be treated with Remeron. It is generally agreed, however, that pharmacological treatment for acute episodes of depression should continue for up to six months or longer. Whether the dose of antidepressant needed to induce remission is identical to the dose needed to maintain euthymia is unknown.

Switching Patients to or from a Monoamine Oxidase Inhibitor

At least 14 days should elapse between discontinuation of an MAOI and initiation of therapy with REMERON™. In addition, at least 14 days should be allowed after stopping REMERON™ before starting an MAOI.

HOW SUPPLIED

[We have made minor modifications to this section.]

REMERON™ (mirtazapine) Tablets are supplied as:

15 mg Tablets - oval, scored, yellow, coated, with "Organon" embossed on one side and "TZ3" on the other side.

Bottles of 30 NDC# 0052-0105-30

Bottles of 100 NDC# 0052-0105-91

Bottles of 500 NDC# 0052-0105-95

Unit Dose, Box of 100 NDC# 0052-0105-90*

30 mg Tablets - oval, scored, red-brown, coated, with "Organon" embossed on one side and "T75" on the other side.

Bottles of 30 NDC# 0052-0107-30

Bottles of 100 NDC# 0052-0107-91

Bottles of 500 NDC# 0052-0107-95

Unit Dose, Box of 100 NDC# 0052-0107-90

*Unit dose packs are provided as a blisterpack with 10 strips, each of which contain 10 tablets.

Store at controlled Room Temperature
20°-25°C (68° - 77°F) [See USP]

Dispense in a tight, light resistant container.

Caution: Federal law prohibits dispensing without a prescription.

Doc LABMRTDP.AE2

REVIEW AND EVALUATION OF CLINICAL DATA

NDA 20-415

Sponsor: Organon

Drug: Remeron (mirtazapine) tablets

Drug Category: Antidepressant

Material Reviewed: NDA Safety Update and Responses to Approvable Letter

Date Submitted: 3/15/96; additional submission 5/10/96

Date Received: 3/18/96; 5/13/96

Medical Officer: Andrew Mosholder, MD

Date of Review: 5/16/96

I. Background

Mirtazepine is an antidepressant compound, chemically similar to mianserin, which acts as an antagonist at serotonergic receptors and alpha-2 presynaptic autoreceptors. On 1/26/96, FDA issued an approvable letter for the Remeron (mirtazepine) NDA. In the approvable letter, a number of revisions were proposed for the drug's labeling. FDA also requested a safety update, to include new reports of serious adverse experiences from clinical trials and any available postmarketing safety data. (The sponsor had submitted an initial safety update on 7/28/95; please refer to Dr. John Balian's clinical review of NDA 20-415 for details.) Other requests included a foreign regulatory status report and commitments from Organon to study a number of clinical issues, including the dose response relationship for depression, dose response and time course of sedative adverse reactions, the use of mirtazepine in children and adolescents, and long term efficacy of mirtazepine.

The approvable letter also included requests relevant to other disciplines (pharmacology, chemistry manufacturing and controls, and biopharmaceutics). This submission includes responses to all of these requests; however, my review will address only the clinical items.

Representatives from the agency met with Organon to discuss the proposed labeling on 4/23/96; also discussed at the same meeting were the Phase IV commitments requested in the approvable letter. Please refer to the meeting minutes for details.

On 4/19/96 the Division requested a more extensive world literature update than had been provided in the 3/15/96 submission. In addition, the Division requested a more detailed worldwide regulatory update (including foreign labeling) on 4/22/96.

The Division faxed a copy of amended labeling to Organon on 5/6/96.

On 5/10/96 the sponsor submitted an additional response to the above requests, including a worldwide literature update and copies of foreign labeling.

II. Safety Update

A. Scope of the Safety Update

The initial safety update covered the period through 1/30/95 and was submitted 7/28/95; please refer to the NDA 20-415 clinical review for details. This submission covers clinical trial data for the period 1/31/95 to 10/31/95. The clinical trials covered by this safety update are noted in the following table. The sponsor did not provide estimates of patient exposure to mirtazepine in these recent trials.

Clinical trials contributing data to this safety update

Study	Description
E1527 U.K.	Randomized, double blind, active control, 6 week (plus 6 mo. extension) parallel group study, 22 centers, patients with severe depression (planned n=60 each for Remeron and fluoxetine), dose range Remeron 15-60 mg/d, fluoxetine 20-40 mg/d. Ongoing.
E1563 Germany	Randomized, double blind, active control, 6 week (plus 20 week extension) study, 16 centers, patients with major depression (planned n=90 each for Remeron and amitriptyline), dose range 15-60 mg/d Remeron, 100-200 mg/d amitriptyline. Ongoing.
E1565 Australia	Randomized, double blind, active control, 6 wk. study, 1 center, patients with major depression (planned n=30 each Remeron and paroxetine), dose range ≥ 15 mg Remeron, ≥ 20 mg paroxetine. Ongoing.
E1659 Holland	Randomized, double blind, active control, 6 wk. study, 32 centers, depressed patients in general practice (planned n=60 each for Remeron and paroxetine), dose range ≥ 15 mg Remeron, ≥ 20 mg paroxetine. Ongoing.
E1600 Sweden	Open label single dose study comparing Remeron pharmacokinetics in poor and extensive debrisoquine metabolizers, n=14, dose 7.5 mg for poor metabolizers and 15 mg for extensive metabolizers. Completed.
22506/France 22507/Germany	Double blind, parallel group, active control, 6 wk. plus long term extension study, inpatients or day patients with depression (n=30 Remeron, n=15 clomipramine, n=15 maprotiline), dose 3-21 mg IV Remeron X 10 days followed by 30-60 mg/d orally; 50-150 mg clomipramine X 10 days followed by 100-200 mg/d orally; 25-150 mg maprotiline IV X 10 days followed by 125-250 mg/d orally. Ongoing.
E22509	Single blind, randomized, 2 way crossover interaction study with lithium, 10 days, single center (n=12 volunteers), lithium 500 mg/d X 10 days with single 30 mg dose of Remeron on day 10. Completed.

In addition to data from these studies, the sponsor has provided postmarketing data from The Netherlands which will be described below.

B. Serious adverse events from clinical trials

There were no deaths in clinical trials during the period covered by this safety update. There were only 2 serious adverse events in clinical trials: patient 361 in study E1527 experienced chest pains but was able to continue his study medication, and patient 367 in the same study developed psychotic symptoms and discontinued from the trial. However, treatment assignments for both subjects remained blinded.

In my opinion, neither case report changes the assessment of mirtazepine's safety profile.

C. Worldwide postmarketing reports

As of 2/1/96, mirtazepine has been marketed only in The Netherlands (since September 1994). There have been a total of 24 postmarketing adverse experience reports comprising 41 individual adverse experiences. An additional 4 reports of mirtazepine overdose have been received, and will be described separately.

The following is an enumeration of these 41 postmarketing adverse experiences, by WHOART term.

<u>Postmarketing Adverse Event</u>	<u>Number</u>
Weight increase	7
Oedema/Oedema dependent	6
Dizziness	3
Headache	3
Somnolence	2
Sweating increased	2
Cellulitis	1
Rash erythematous	1
Arthralgia	1
Convulsions	1
Hypoesthesia	1
Muscle contractions involuntary	1
Depression aggravated	1
Insomnia	1
Paroniria	1
Mouth dry	1
Nausea	1
SGOT increased	1
SGPT increased	1
Hypoglycemia	1
Hypotension	1
Pharyngitis	1
Urinary incontinence	1
<u>Fever</u>	<u>1</u>
Total	41

The sponsor provided summaries of each of the postmarketing case reports. I will comment on a few of the noteworthy cases here.

Case # 9500024 involved a 25 year old female who developed a generalized rash and eosinophilia associated with mirtazepine and carbamazepine use; the rash and eosinophilia later recurred when mirtazepine was reintroduced. Rash was a "frequent" (i.e., incidence $\geq$ 1%) event in the premarketing clinical trial database. The draft labeling for Remeron contraindicates the drug in cases of hypersensitivity.

Case # 9500004 described a 32 year old male who experienced a possible seizure with mirtazepine use for 3 months; details were lacking, however. Only one seizure was reported in premarketing clinical trials, as noted in the draft labeling under Precautions.

The report of liver enzyme elevations (Case 9500009) involved a patient with chronic hepatitis B; the enzymes normalized while the patient continued Remeron.

There were a number of cases of edema reported, as shown above; in short term domestic controlled trials, edema was reported in 1.3% and 0.3% of mirtazepine and placebo patients, respectively.

Of interest is the absence of reports of blood dyscrasias. Organon argues that this casts doubt on the causal relationship of mirtazepine to agranulocytosis, based on the assumption that a highly regarded postmarketing surveillance program is in place in The Netherlands, and that accordingly one can assume that any cases of agranulocytosis would have been reported. In fact, a rough guide to the efficiency of postmarketing surveillance in various countries can be obtained from the data which Organon submitted regarding reports of

blood dyscrasias with mianserin, a compound closely related to mirtazepine (see pg. 92 of the 12/2/94 submission to NDA 20-415). This data describes the number of blood dyscrasia spontaneous reports per million daily doses of mianserin sold in each country. Reporting rates ranged from 0.09 reports/million daily doses (France, Belgium) to 9.3 reports per million daily doses (New Zealand). The Netherlands reporting rate was intermediate at 1.2 per million daily doses.

Overdose reports

There have now been 4 cases of mirtazepine overdose reported with marketed drug; three of these were reviewed in Dr. Balian's clinical review of the Remeron NDA. The following summarizes one additional case submitted with this safety update. In my opinion, this case report does not materially affect the assessment of mirtazepine's overdose toxicity.

Age (yrs)	Sex	Overdose (mg)	Concomitant drugs	Comments
34	m	975	Unknown benzodiazepine, 30 tablets	Comatose, pinpoint pupils; received gastric lavage, benzodiazepine antagonist and forced diuresis. Discharged after 3 days.

D. World Literature

The sponsor submitted a bibliography of literature reports covering the period from the original NDA to the present (1994 to 1996). The sponsor warrants that their literature search disclosed no reports that would adversely affect the conclusions about Remeron's safety.

No copies of the articles were provided in the submission, but some of the references did include abstracts. My own review of these did not disclose any significant new information. Many (but not all) of the clinical studies described in the publications had been submitted with the NDA.

E. Worldwide Regulatory Status

Remeron is marketed only in The Netherlands. It has been approved by the European Proprietary Medicinal Products organization, and by regulatory authorities in Argentina, Austria, Brazil, Denmark, Finland, Germany, Greece, Ecuador, Peru, Spain (pending price negotiations) and Sweden. Launch is planned in Finland, Denmark, Germany and Greece in the near future. Organon reports that no negative regulatory action has been taken on Remeron.

The 5/10/96 submission included English versions of labeling for the following countries: The Netherlands, Finland, Denmark, Germany, Argentina, Austria, Greece, Spain, Sweden, Brazil, Ecuador and Peru. My review of this labeling did not disclose any important new clinical information. Many of the foreign labels are quite similar, and place less emphasis on the cases of agranulocytosis than the proposed U.S. labeling. The Swedish labeling states that in vitro studies show that mirtazepine may inhibit the cytochrome P450 enzymes 1A2, 2D6, and 3A4. This is a stronger conclusion than the description in U.S. draft labeling, which states that in vitro studies have shown that mirtazepine is not a potent inhibitor of these

enzymes, although it is a substrate (see under Precautions-Drug Interactions).

Labeling for a number of countries (e.g., Finland) states that patients should avoid driving, a somewhat stronger statement than in the proposed U.S. labeling.

F. Other clinical requests from the Approvable Letter

Phase IV commitments were discussed at the meeting 4/23/96. In the 5/10/96 submission, Organon has agreed to conduct a fixed dose response/somnolence study and a relapse prevention study. It was mutually agreed at the April meeting that a pediatric study would not be required.

III. Labeling

Organon has objected to many aspects of the approvable letter labeling, most notably the agency's proposed black box warning regarding agranulocytosis associated with mirtazepine. On April 23, 1996, representatives from Organon met with FDA staff to discuss Remeron's labeling. Please refer to the minutes of this meeting for details. Following that discussion, the Agency faxed a revised version of labeling to Organon on 5/6/96. In their response 5/10/96, Organon accepted the proposed labeling with only minor corrections (see cover letter 5/10/96).

IV. Miscellaneous

On 4/29/96, Organon faxed a letter (not submitted to the NDA) regarding the issue of automobile accidents. The sponsor argued in the fax that accidents are common and that the occurrence of motor vehicle accidents during clinical trials with mirtazepine (4 accidents among 2796 patients) was not unexpected. They requested that the somnolence precaution section not be bolded.

V. Conclusions and Recommendations

The absence of postmarketing reports of agranulocytosis from The Netherlands does not adequately refute the finding from clinical trials of an incidence of roughly 1 per thousand patients exposed, notwithstanding the admittedly large confidence interval on this estimate; to me, it seems quite possible that cases may not have been reported. In my opinion, the Remeron labeling should carry a boxed warning about agranulocytosis. This would have implications for how the drug could be promoted (under CFR 202.1) and would make it less likely that prescribing physicians would overlook this important safety consideration.

I do not find the sponsor's arguments for un-bolding the somnolence precaution persuasive. The controlled clinical trial data point to a powerful sedating effect of mirtazepine, as described in Dr. Balian's clinical review. In two of the four accidents involving mirtazepine treated patients, somnolence was considered a contributing factor.

The sponsor's minor corrections to the 5/6/96 amended labeling are acceptable.

There is no new clinical data in the safety update which would alter the previous conclusions about the safety of mirtazepine, and from a clinical standpoint the drug may be approved for the treatment of depression.

As a postmarketing surveillance commitment, I recommend that the sponsor submit cases of adverse hematologic events as 15 day reports, rather than with the NDA periodic

reports. This will facilitate surveillance for cases of agranulocytosis. The same request should be applied to serious hepatic adverse events.

 5/16/96
Andrew Mosholder, MD
Division of Neuropharmacologic Drug Products

Orig. NDA 20-415
HFD-120 Div. File
HFD-120 TLaughren/PDavid/AMosholder

5-20-96

I agree that Remeron can
now be approved. ~~See~~
my memo to the file for
more detailed comments.

Thomas P. Laughren, MD
GL, PDP

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS
REVIEW OF CHEMISTRY AND MANUFACTURING CONTROLS

NDA 20,415

	<u>letterdate</u>	<u>stampdate</u>	<u>rec'd by chemist</u>	<u>COMPLETED</u>
INITIAL SUBMISSION:	26-JAN-95	30-JAN-95	30-JAN-95	5-MAY-95
AMENDMENT:	15-MAR-96	15-MAR-96	19-MAR-96	05-APR-96

CHEMIST REVIEW: # 5

SPONSOR: ORGANON

REVIEW CHEMIST: M.Zarifa, Ph.D

**ADDRESS: 375 Mt. Pleasant Avenue
West Orange, NJ 07052**

PRODUCT NAME:

Proprietary:

REMERON

USAN:

Mirtazapine

Code Name/Number:

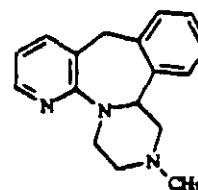
ORG 3770

DOSAGE FORM/ROUTE OF ADMINISTRATION: 15 mg and 30 mg Tablets/Oral

PHARMACOL.CATEGORY/PRINCIPAL INDICATION: Depression

STRUCTURAL FORMULA & CHEMICAL NAME:

C₁₇H₁₉N₃ Mol. Wt. 265.36



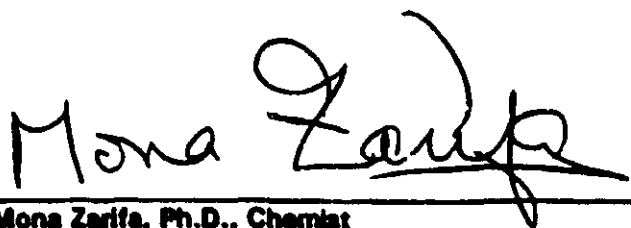
1,2,3,4,10,14b-hexahydro-2-methylpyrazino[2,1-a]pyrido[2,3-c]benzazepine

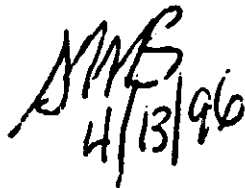
REMARKS: In this amendment the sponsor responds to the Approvable Letter dated January 26, 1996. For CMC, the sponsor provides a 24-month update of stability data and requests an expiry date of 36 months based on the provided data and on the supportive data in the original submission. The data provided are adequate but do not support more than the 24-month expiration date granted in the Approvable Letter.

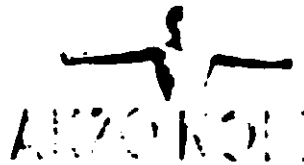
CONCLUSIONS & RECOMMENDATIONS: RECOMMEND THAT NDA 20-415 FOR ORG 3770 TABLETS IS APPROVED WITH THE RESTRICTION OF EXPIRY DATE TO 24 MONTHS AT THIS TIME. THE EXTENSION OF EXPIRATION DATE TO 36 MONTHS MAY BE CONSIDERED ONLY POST APPROVAL.

cc: ORIG: NDA
HFD-120/Div. File
HFD-120/CSO/P.David
HFD-120/SBtum/MZarifa
WNT:

filename: N020415.004


Mona Zarifa, Ph.D., Chemist


4/13/96



CONFIDENTIAL

Organon Inc.

March 15, 1996

Paul Leber, M.D., Director
Division of Neuropharmacological Drug Products
Center for Drug Evaluation and Research (HFD-120)
Woodmont II Building, 4th Floor
1451 Rockville Pike
Rockville, MD 20857



Re: **NDA 20-415**
REMERON™ (mirtazapine) Tablets
Response to FDA Approvable Letter

Dear Dr. Leber:

Reference is made to Organon Inc. NDA No. 20-415 for Remeron™ (mirtazapine) Tablets, originally filed on April 29, 1994 and resubmitted on January 26, 1995, to FDA approvable letter for the NDA dated January 26, 1996, and to our acknowledgment, on February 7, 1996, of receipt and intention to reply to issues raised in the approvable letter. We also requested a meeting with the Division to discuss disagreements with some aspects of the proposed revisions to the labeling and a meeting to discuss feasibility and design issues with the requested Phase IV clinical trial commitments. Reference is further made to teleconferences between Mr. P. David of the Division and Dr. L. Tran of this firm on February 21, 1996 and March 6, 1996, during which it was agreed that a detailed response to the approvable letter and proposed agendas for the requested meeting(s) be submitted as soon as possible, in preparation for a meeting with the Division on April 8, 1996 at 8:00 a.m. in the Neuropharmacological Division conference room. Accordingly, we herewith provide such information. For ease of review, each FDA item will be presented first, followed by our response in italics.

CLINICAL

1. Labeling

Accompanying this letter (ATTACHMENT 2) is the Agency's proposal for the labeling of Remeron™. We believe it presents a fair summary of the information available on the benefits and risks of mirtazapine. Please use the proposed text verbatim.

We have proposed a number of changes to the draft labeling submitted in your August 21, 1995 labeling amendment, and explanations for these changes are provided in the bracketed comments embedded within the proposed text. Division staff would be happy to discuss these proposed changes in detail, and we would be happy to meet with you to discuss any disagreements you might have with any part of the proposed labeling format and content.



Organon Inc.
2700 Rockledge Avenue
Kenilworth, NJ 07033
Tel: 201-261-6000
Fax: 201-261-6001
E-Mail: info@organon.com

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March 15, 1996
Remeron (mirtazapine) Tablets, NDA 20-415
Response to FDA Approvable Letter
Page 2

Response:

After careful review and thoughtful consideration of the proposed text, differences in opinion exist for several critical issues especially with regards to the adverse events profile. Therefore, we requested a meeting with the Division on April 8, 1996 to discuss a mutual resolution. Thus, in Attachment 1, we provide a proposed agenda for the labeling portion of the meeting, the proposed changes to the Agency's version of the labeling, and supporting documentation for these proposed changes. The changes to the Agency's proposed text are provided in a redline/strike-out format for ease of review. Justifications are provided side-by-side to the proposed changes. As requested by Mr. David by phone, a computer disk copy of the proposed package insert is also provided in this submission.

2. Safety Update

Our assessment of the safety of mirtazapine is based on our review of all safety information provided in your original and subsequent submissions, including your safety update (July 28, 1995 amendment). This original review is based on an integrated database comprising studies completed prior to December, 1993, for which no more data will be forthcoming, and on any additional serious events reported from a completed European study (86017) and from five ongoing foreign studies, with a cutoff date of approximately July, 1995. Please provide a final serious events update to include serious adverse events up to a more recent cutoff date.

In addition, please provide an updated postmarketing adverse event report from the Netherlands and any other countries where Remeron™ is now available. In order to help us in interpreting this information, please provide details on the methodology for postmarketing surveillance in those countries for which such reports are available. In particular, it would be helpful to know what information is available regarding the numbers of patients exposed and the extent of exposure, how this information is determined, what mechanism is used for reporting and whether or not follow-up on cases is feasible.

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March 15, 1996
Remeron (mirtazapine) Tablets, NDA 20-415
Response to FDA Approvable Letter
Page 3

Response:

A final safety update report, including data to the cut-off date of October 31, 1995, is provided in Attachment 2. This report includes serious adverse events data from 8 ongoing foreign studies as well as postmarketing data since the 120 day safety update.

An updated post-marketing surveillance (PMS) report covering the period from introduction in September 1994 to February 1, 1996 is also provided in Attachment 2. The PMS data include reports directly from individual physicians or other health care professionals, reports from regulatory authorities, and comprehensive literature searches (Biosis, Current Content, Derwent Drug File, Embase and Medline) by the Company for case reports published in medical/professional journals. In general, Organon tries to conduct follow-up on all serious adverse events cases in an attempt to collect as many relevant data as possible.

Exact information regarding the number of patients exposed and extent (dose and duration) of exposure for Remeron™ is not readily obtainable. In the provided PMS report, the extent of Remeron™ used is estimated from prescription data from Intercontinental Medical Statistics (IMS), and from sales volume from the IMS Dutch Pharmaceutical Index of sales volume to pharmacies and Organon sales figures. Using the sales figure, the number of treatment courses is calculated assuming 30 mg/day treatment for 2 months duration. To date, more than patients have been treated with Remeron based on the IMS prescription data, and at least patients are expected to have been exposed to the product based on IMS Dutch Pharmaceutical Index and Organon sales figures.

It should be remarked that post-marketing surveillance in the Netherlands in the recent past has identified a number of important drug safety issues before they were noted in other countries (see references attached to the PMS report). This good track record of drug safety signal perception is reassuring to the effect that the occurrence of serious Remeron-associated adverse events is unlikely to be missed in the Netherlands. In view of this, we note that no additional cases of agranulocytosis or blood dyscrasias have been reported since the drug was introduced in September 1994.

CONFIDENTIAL

March 15, 1996
Remeron (mirtazapine) Tablets, NDA 20-415
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Page 4

3. Regulatory Status Update

Please provide any new information on the regulatory status of mirtazapine worldwide, i.e., information available subsequent to the regulatory status update provided in your September 26, 1995 amendment.

Response:

Remeron™ is currently marketed in the Netherlands. It is approved for marketing in Argentina, Austria, Brazil, Denmark, Finland, Germany, Greece, Peru, Spain (scientific approval with pending pricing negotiations), and Sweden. Argentina, Brazil, Denmark, Germany, Greece, Spain and Sweden are the new approvals since the September 26, 1995 Amendment to the NDA. Remeron™ is expected to be introduced into the Finnish, Danish, German and Greek markets in the next few months. As the Agency was previously informed, the product received positive opinion from the European Proprietary Medicinal Products (CPMP) in September 1995; therefore, we expect to work towards approval in all CPMP member states in the course of 1996.

4. Exploration of Dose Response for Effectiveness

4
2/15/96

While your development program for mirtazapine has identified an effective dose range for this drug, it has not adequately addressed dose response within this range. Consequently, we ask that you commit to conducting, subsequent to approval as a Phase 4 commitment, additional studies to properly explore the 15-45 mg range. The Division will be happy to collaborate with your clinical and statistical staff in the design of such a program.

Response:

As stated by the Division, an effective dose range of 15-45 mg was identified for mirtazapine in our clinical trials. In clinical practice, the drug is expected to be titrated by physicians until a desired response is obtained. Thus, we question the utility of additional dose-response information in an already established effective dose range.

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Response to FDA Approvable Letter

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5. Exploration of Dose Response and Time Course for Sedative Effects of Mirtazapine

Phase 4

One of the more troublesome of the common adverse events associated with mirtazapine use is its somnolent properties. What is unknown from the available data is the dose dependency for this event and whether or not and to what extent there may be adaptation. This is a sufficiently important clinical concern that we ask your commitment to conducting, subsequent to approval, a study that provides data pertinent to this issue. It may be possible to combine this effort and an exploration of dose/response for efficacy into one study. Again, the Division will be happy to collaborate with your clinical and statistical staff in the design of such a program.

Response:

We acknowledge your comment about the sedative effects of mirtazapine. We wish to discuss design issues with the Division before committing to embark on the conduct of such study. Provided in Attachment 3 is a preliminary outline of a study to initiate our discussion. We request discussion about this study after completion of the labeling portion of the meeting on April 8, 1996.

6. Pediatric Depression Studies

Phase 4

Since it is likely that mirtazapine, once marketed, will be used in children and adolescents with depression, we ask that you commit to conducting, subsequent to approval as a Phase 4 commitment, studies in this population in order to provide the safety and efficacy data needed to support such use. A useful starting point would be to obtain some pharmacokinetic data in depressed children and adolescents. The Division will be happy to collaborate with your clinical and statistical staff in your design of such a program.

Response:

Organon does not intend to market mirtazapine in the pediatric population and therefore does not wish to conduct safety and efficacy trials in this patient population. Additionally, if mirtazapine's labeling was to contain a boxed warning for agranulocytosis, we believe this will limit the drug's use and it will become a treatment of last resort; therefore, we question the need to conduct trials in this patient population.

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7. Long-Term Efficacy Studies

Phase 4
Although your NDA for Remeron™ documents the effectiveness of mirtazapine as a treatment of acute depressive illness over an interval of 6 weeks, it fails to provide necessary to sustain its antidepressant effects over the full duration (presumed to be 6 months to a year) of an acute depressive episode. However, because it is widely assumed that continued treatment of symptomatically remitted patients reduces their risk of relapse, the proposed labeling for Remeron™ recommends that treatment be continued, presumably at the same doses as those used to induce remission, for intervals of several months or longer following the acute episode for which treatment was initiated. These labeling recommendations notwithstanding, the conditions of extended use that maximally decrease the risk of relapse are unknown. Accordingly, we ask for your commitment to conduct, subsequent to approval as a Phase 4 commitment, a controlled trial to evaluate the conditions affecting mirtazapine's capacity to reduce the risk of relapse in acutely remitted patients. Because the methods for conducting such a study of the type described are still in evolution, the Division will be happy to collaborate with your clinical and statistical staff should questions concerning its design and/or conduct arise.

Response:

We acknowledge your request to conduct a study to explore the conditions of extended use that maximally decrease the risk of relapse. However, if mirtazapine's labeling was to contain a boxed warning for agranulocytosis, we believe this will limit the drug's use and it will become a treatment of last resort; therefore, we question the need to conduct a highly expensive long term trial (~3 years for completion) for this drug.

PHARMACOLOGY

1. Pregnancy Category C

The segment I and II reproduction studies in rats revealed a decrease in pup survival, and also a decrease in pup weights (segment III only). In the segment II study (teratology) there was an increased incidence of post-implantation loss. Because it cannot be determined whether or not these findings were related to effects of the drug on the developing fetus in utero or were secondary to postnatal drug effects on the dams and/or pups, we have labeled Remeron™ pregnancy category C.

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Response:

We accept this classification

2. Mouse carcinogenicity study

The CDER Carcinogenicity Assessment Committee (CAC) voted that a maximum tolerated dose (MTD) was not achieved in the 18 month mouse carcinogenicity study, and concluded that exposure data are needed before a determination about the adequacy of the study may be made. We request, as a Phase 4 commitment, that you agree to conduct a three month dietary administration study in mice to address this issue. The study should be designed to examine the plasma AUC's of parent drug and all major metabolites, particularly those found in both humans and mice. Doses should include the high dose of 200 mg/kg used in the carcinogenicity study and also two or more higher doses, chosen to attempt to determine an actual MTD. It is hoped that the information obtained from such a study will permit us to make a decision about whether or not the high dose of 200 mg/kg provided adequate exposure of drug and metabolites relative to human exposure to consider the study valid. It should also provide us with information about what fraction of an MTD was actually achieved. Depending upon the outcome of that three month study, additional Phase 4 studies may be required. Our staff will be happy to assist you in the design of this study if you wish.

Response:

It is not known at this time whether there is saturation of absorption when high doses are given to the mice; therefore, we plan to first perform a pilot 2-week dietary study with 200, 1000, and 10,000 mg/kg mirtazapine. Results of this study will be available in June 1996, and will be submitted to the Agency for review. Depending on the results of this study, we will conduct a three month dietary administration study in the mice as necessary.

MANUFACTURING AND CONTROLS

1. 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. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

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Response:

We commit to continuing cooperation with the FDA laboratory during its validation of the regulatory methods for Remeron.

2. Expiration Date

Please note that, at this time, we are only approving a 24-month expiry date for the drug product based on the 18-month stability data which was provided.

Response:

Remeron™ tablets demonstrate little loss of activity/potency in our stability program over the period upto 24 months. This data clearly supports an expiration dating period of at least 3 years for the product as requested in our NDA. Thus, we herewith request your re-consideration to approve a 36-month expiry date for the product. An updated stability report, providing data up to 24 months, is provided in Attachment 4.

BIOPHARMACEUTICS

1. Phase 4 Commitments

We request that you perform in vitro enzymatic experiments on mirtazapine with other inhibitors or substrates of CYP1A2 (e.g., theophylline and fluvoxamine), CYP2D6 (e.g., tricyclic antidepressants and selective serotonin reuptake inhibitors), and CYP3A (e.g., ketoconazole and erythromycin), and submit these results to the Agency. It is possible that you have already conducted studies that will adequately address these issues, e.g., some pertinent in vitro data were present in a preliminary manner at the October 16, 1995 meeting of the Psychopharmacological Drugs Advisory Committee meeting. However, we ask that you submit a more complete report on these studies.

Response:

We have conducted an in vitro enzymatic inhibition study with mirtazapine using the selective enzyme inhibitors fluvoxamine (CYP1A2), fluoxetine (CYP2D6) and ketoconazole (CYP3A) as comparative agents. Mirtazapine was found to be a competitive inhibitor of CYP1A2, CYP2D6 and CYP3A, but was much less potent an inhibitor than the cytochrome P450 inhibitors fluvoxamine (CYP1A2), fluoxetine (CYP2D6) and ketoconazole (CYP3A). This suggests that mirtazapine is unlikely to play a significant interactive role at the cytochrome P450 level with regards to metabolism of coadministered drug. A copy of this study report is provided in Attachment 5.

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2. **Dissolution Specifications**

We ask that you agree to the following recommendation by the Division of Biopharmaceutics for a dissolution method and specification for all tablet strengths:

Apparatus:
Paddle Speed:
Medium:
Specifications:

Response:

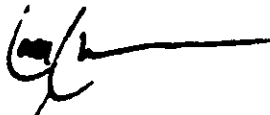
We agree to revising the dissolution method and specification for all tablet strengths as described above.

As the labeling issue still has yet to be resolved, final printed labeling and draft introductory promotional materials for this product can not yet be submitted. We will submit these materials as soon as possible after resolution of the package insert.

Please note that Organon Inc. regards this application and all correspondence related thereto as confidential, trade secret and proprietary information and hereby claims protection from disclosure under the applicable sections of 18 U.S.C. and 21 CFR.

We look forward to a productive meeting with the Division on April 8, 1996. Should you have any questions regarding this submission, please contact the undersigned at (201) 325-4837.

Sincerely,



Loan T. Tran, Pharm. D
Assistant Director
Regulatory Affairs

Enclosures: Volume 1, Pages 0001- 0339; Volume 2, Pages 0001-0275

7 Desk copies to Mr. Paul David, Project Manager
2 NDA copies

Submitted to NDA 20-415 via Federal Express No. 6586652494

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Justification for Removal of Boxed Warnings for Agranulocytosis

The Agency has proposed a bolded box warning for the rare occurrence of agranulocytosis/severe neutropenia observed in Remeron™ (mirtazapine) clinical trials (crude incidence of approximately 1 in 1000 with a confidence limit of 0.2 to 3 cases per 1000). We disagree with this proposal and believe our proposed bolded text for such rare occurrences is adequate. Our reasons are as follows:

- ▶ We believe that the true incidence of agranulocytosis/severe neutropenia associated with Remeron™ may be lower than 1 in 1000. In clinical trials with 2796 patients treated with Remeron™, three cases of severe neutropenia (two of which were agranulocytosis) were observed. In one case, severe neutropenia was detected without development of symptoms of agranulocytosis. In another, agranulocytosis was confounded by Sjögren's Syndrome, an autoimmune disease with hematological abnormalities such as leukopenia. Only in one case was there an agranulocytosis without confounding factors. In our opinion, these cases are quite different, should not be lumped together, and may not all be representative of the general depressed patient population. For instance, since Remeron™ was introduced in the Netherlands from September 1994 up to February 1, 1996, more than _____ patients (IMS prescription data) to at least _____ patients (sales figures) have been treated without any reported cases of agranulocytosis (please refer to attached postmarketing surveillance report). This lends support to our belief that the true incidence of agranulocytosis is lower than 1 in 1000 and that the incidence may be towards the lower limit of the confidence interval of the crude incidence that the Agency calculated based on the clinical trials population.
- ▶ Additionally, we believe that the incidence of agranulocytosis seen for Remeron™ may not be different from that of other antidepressant drugs currently marketed. In the opinion of an independent hematology expert (Dr. Gerson) who presented at the October 16, 1995 FDA Psychopharmacologic Drugs Advisory Committee meeting, the incidence of agranulocytosis associated with the use of tricyclic antidepressants is between 0.7 to 3 per 1000 (these figures are not derived from controlled clinical trials.) None of these drugs have boxed warnings or even bolded warnings for agranulocytosis. It should be noted again that in a Remeron™ trial with imipramine as a positive control, an imipramine patient developed agranulocytosis.
- ▶ Finally, we believe that over-labeling for this rare event will discourage physicians' use of Remeron™ and limit its access to patients who may benefit from the novel mechanism of action of Remeron™. We again refer to the FDA Psychopharmacologic Drugs Advisory Committee, whose members voted unanimously to approve the drug for first line therapy. A boxed warning would likely relegate Remeron™ to a treatment of last resort.

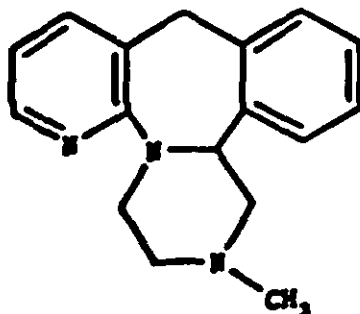
REMERON™

(mirtazapine) Tablets

Justification for Proposed Changes:

DESCRIPTION

REMERON™ (mirtazapine) is an ~~is~~ structurally novel antidepressant for oral administration. ~~It has~~ with a tetracyclic chemical structure unrelated to selective serotonin reuptake inhibitors, tricyclics or monoamine oxidase inhibitors (MAOI). Mirtazapine belongs to the piperazino-azepine group of compounds. It is designated 1,2,3,4,10,14b-hexahydro-2-methylpyrazino [2,1-a] pyrido [2,3-c] benzazepine and has the empirical formula of $C_{17}H_{19}N_3$. Its molecular weight is 265.36. The structural formula is the following and it is the racemic mixture:



Mirtazapine is a white to creamy white crystalline powder which is slightly solution in water.

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REMERON™ is supplied for oral administration as scored film-coated tablets containing 15 or 30 mg of mirtazapine. Each tablet also contains corn starch, hydroxypropyl cellulose, magnesium stearate, colloidal silicon dioxide, lactose, and other inactive ingredients.

CLINICAL PHARMACOLOGY

Pharmacodynamics

The mechanism of action of the antidepressant REMERON™ (mirtazapine) is believed to be associated with its potentiation of noradrenergic activity in the CNS, as with other antidepressants, is unknown.

Preclinical studies have shown that mirtazapine acts specifically as an antagonist at central presynaptic α_2 adrenergic inhibitory autoreceptors, an action that is postulated to result in an increase in central noradrenergic and serotonergic activity.

Mirtazapine is a potent antagonist of 5-HT₂ and 5-HT_{1B} receptors. Mirtazapine has no significant affinity for the 5HT_{1A} and 5HT_{1C} receptors.

Mirtazapine is a potent antagonist of histamine (H₁) receptors, a property that may explain in the sedative effects seen in patients receiving this drug.

• We request wordings that are similarly approved for other antidepressants, eg. Effexor (venlafaxine).

• This is a more accurate description of mirtazapine's pharmacology. Please refer to the attached SDGRR 3966 (Reference #1) and publications (References #2, 3).

• This is a complete description of mirtazapine activity with the serotonin receptors. Please refer to SDGRR 2488, NDA Volume 2.14, page 0002. (de Graaf JS. Comparative CNS pharmacology of Org 3770.)

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Adapt. w/ a risk

Mirtazapine is a ~~weak~~ moderate peripheral α_1 adrenergic antagonist, a property that may explain orthostatic hypotension and dizziness reported in association with its use.

Mirtazapine is a ~~weak~~ ^{moderate} antagonist at muscarinic receptors, a property that may explain anticholinergic side effects.

Pharmacokinetics

REMERON™ (mirtazapine) is rapidly and completely absorbed following oral administration and has a half-life of about 20-40 hours. Peak plasma concentration are reached within about 2 hours following an oral dose. The presence of food in the stomach has a minimal effect on both the rate and extent of absorption and does not require a dosage adjustment.

Mirtazapine is extensively metabolized by cytochrome P450 enzymes, primarily 2D6 and 1A2 and to a lesser extent 2C9 and 3A, and ~~the following~~ ^{major} pathways of biotransformation are demethylation and hydroxylation followed by glucuronidation. ^{In vitro} data from human liver microsomes indicate that cytochrome 2D6 and 1A2 are involved in the biotransformation of mirtazapine, whereas cytochrome 3A is considered to be responsible for the formation of the 8-hydroxy and 8-oxide metabolites. Mirtazapine has an absolute bioavailability of about 50%. It is eliminated predominantly via urine (75%) with 15% in feces. Major pathways of biotransformation are demethylation and

• Mirtazapine is a weak α_1 antagonist, as indicated by its low binding constant, pK_i 6.3-6.6. This is supported by the low incidence of orthostatic hypotension in U.S. controlled clinical trials: Remeron (1.1%), placebo (0.6%), amitriptyline (5.2%)

• Mirtazapine is a weak muscarinic antagonist, as indicated by its low binding constant, pK_i 6.1. This is supported by the low incidence of anticholinergic S.E. in U.S. controlled clinical trials: Remeron (23.4%), placebo (12.7%), amitriptyline (81.7%)

• This provides a more accurate description of the metabolism of mirtazapine and the P450 isoenzymes involved. Please refer to report SDGRR 4077 submitted to the NDA on May 8, 1995. (Vos RME. Characterization of human cytochrome P450 isoenzymes involved in the in vitro metabolism of Org 3770.)

hydroxylation followed by glucuronide conjugation. Several unconjugated metabolites possess pharmacological activity but are present in the plasma at very low levels. The (-) enantiomer has an elimination half-life that is approximately twice as long as the (+) enantiomer and therefore achieves plasma levels that are about three times as high as that of the (+) enantiomer.

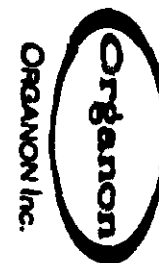
Plasma levels are linearly related to dose range of 15 to 80 mg. The mean eliminated half-life of mirtazapine after oral administration ranges from approximately 20-40 hours across age and gender subgroups, with females of all ages exhibiting significantly longer elimination half-lives than males (mean half-life of 37 hours for females vs 26 for males). Steady state plasma levels of mirtazapine are attained within 5 days, with about 50% accumulation (accumulation ratio = 1.5).

Mirtazapine is approximately 85% bound to plasma proteins over a concentration range of 0.01 to 10 g/mL.

Population Subgroups

Liver Disease - Following a single 15 mg oral dose of mirtazapine, the oral clearance of mirtazapine was decreased by approximately 30% in hepatically impaired patients compared to subjects with normal hepatic function. Caution is indicated in administering REMERON™ to patients with compromised hepatic function (see Precautions and Dosage and Administration).

Renal Disease - Following a single 15 mg oral dose of mirtazapine, patients with moderate [glomerular filtration rate (GFR) = 11-39 mL/min/1.73 m²] renal impairment had reduction



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in mean oral clearance of mirtazapine of about 30% and 50%, respectively, compared to normal subjects. Caution is indicated in administering REMERON™ to patients with compromised renal function (see Precautions and Dosage and Administration).

Elderly Patients - Following oral administration of mirtazapine 20 mg/day for 7 days to subjects of varying ages (range, 25-74), oral clearance of mirtazapine was reduced in the elderly compared to the younger subjects. The differences were most striking in males, with a 40% lower clearance in elderly males compared to younger males, while the clearance in elderly females was only 10% lower compared to younger females. Caution is indicated in administering REMERON™ to elderly patients (see Precautions and Dosage and Administration).

Smokers - Cigarette smoking increased the mean oral clearance of mirtazapine by about 30%.

Clinical Trials Showing Effectiveness

The efficacy of REMERON™ (mirtazapine) as a treatment of depression was established in four placebo-controlled, 6-week trials in adult outpatients meeting DSM-III criteria for major depression. Patients were titrated with mirtazapine from a dose range of 10 mg up to 35 mg/day. Overall, these studies demonstrated mirtazapine to be superior to placebo on at least three of the following four measures: 21-Item Hamilton Depression Rating Scale (HDRS) total score; HDRS Depressed Mood Item; CGI Severity score; and Montgomery and Asberg Depression Rating Scale (MADRS). Superiority of mirtazapine over placebo was also found for certain factors of the HDRS,

- 7310
- We do not know the source of this information. Smoking effect was not presented or officially studied in our NDA.

- CLP
- This is an error.

- OK
- Consistency of presentation with the previous statement.

(e.g., ~~anxiety~~ anxiety/somatization factor and sleep disturbance factor). The mean mirtazapine dose for patients who completed these four studies ranged from 21 to 32 mg/day. A fifth study of similar design utilized a higher dose (up to 50 mg) per day and also showed effectiveness.

Examination of age and gender subsets of the population did not reveal any differential responsiveness on the basis of these subgroupings.

INDICATIONS AND USAGE

REMERON™ (mirtazapine) Tablets are indicated for the treatment of depression.

The efficacy of REMERON™ in the treatment of depression was established in six week controlled trials of outpatients whose diagnoses corresponded most closely to the Diagnostic and Statistical Manual of Mental Disorders - 3rd edition (DSM-III) category of major depressive disorder (see CLINICAL PHARMACOLOGY).

A major depressive episode (DSM-IV) implies a prominent and relatively persistent (nearly every day for at least 2 weeks) depressed or dysphoric mood that usually interferes with daily functioning, and includes at least five of the following nine symptoms: depressed mood, loss of interest in usual activities, significant change in weight and/or appetite, insomnia or hypersomnia, psychomotor agitation or retardation, increased fatigue, feelings of guilt or worthlessness, slowed thinking or impaired concentration, a suicide attempt or suicidal ideation.

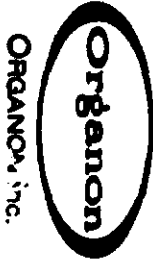
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The antidepressant effectiveness of REMERON™ (mirtazapine) in hospitalized depressed patients has not been adequately studied.

The effectiveness of REMERON™ in long-term use, that is, for more than 6 weeks, has not been systematically evaluated in controlled trials. Therefore, the physician who elects to use REMERON™ for extended periods should periodically evaluate the long-term usefulness of the drug for the individual patient.

CONTRAINDICATIONS

REMERON™ (mirtazapine) Tablets are contraindicated in patients with a known hypersensitivity to mirtazapine.



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WARNINGS

Agranulocytosis

In premarketing clinical trials, two (one with Sjögren's Syndrome) out of 2,796 patients treated with REMERON™ (mirtazapine) Tablets developed agranulocytosis (absolute neutrophil count (ANC) < 500/mm³ with associated signs and symptoms, e.g., fever, infection, etc.) and a third patient developed severe neutropenia (ANC < 500/mm³ without any associated symptoms). For these three patients, onset of severe neutropenia was detected on days 9, 17, 14, and 61 of treatment, respectively. All three patients recovered after REMERON™ was stopped. These three cases yield a crude incidence of severe neutropenia (with or without associated infection) of approximately 1.1 per thousand patients exposed, with a very wide 95% confidence interval, i.e., 2.2 cases per 10,000 to 3.1 cases per 1000. No cases of agranulocytosis or severe neutropenia have been reported in post-marketing experience with the drug in the Netherlands, where more than 9,000 patients have been treated. If a patient develops a sore throat, fever, stomatitis or other signs of infection, along with a low WBC count, treatment with REMERON™ should be discontinued and the patient should be closely monitored.

- We request removal of the boxed warning, and believe our proposed bolded text for this rare event is adequate. A full discussion justifying our request is provided in front of this proposed labeling package. Briefly:

-We believe the incidence may be lower than the crude incidence of 1 in 1000 calculated for the clinical trials. The cases reported in the text are quite different and may not all be representative of the general depressed patient population. For instance, since the product was introduced in the Netherlands from September 1994 to February 1, 1996, more than 9,000 to 14,000 patients have been treated without any report of agranulocytosis.

-We believe the incidence of agranulocytosis seen for Remeron™ may not be different than that of other marketed antidepressants.

-Over-labeling for this rare event will discourage physicians use of Remeron™, limit its access to patients who may benefit from its novel mechanism of action, and likely relegate it to a treatment of last resort. This is not consistent with the FDA Advisory Committee's recommendation, whose member voted unanimously to approve the drug for first line therapy.

- Incorrect information. Refer to 9/14/95 General Correspondence Submission to NDA. Volume 1, Page 0026.
- Incidence too crude to provide a true number.



MAO Inhibitors

In patients receiving other antidepressants in combination with a monoamine oxidase inhibitor (MAOI) and in patients who have recently discontinued an antidepressant drug and then are started on an MAOI, there have been reports of serious, and sometimes fatal, reactions, e.g., including nausea, vomiting, flushing, dizziness, tremor, myoclonus, rigidity, diaphoresis, hyperthermia, autonomic instability with rapid fluctuations of vital signs, seizures, and mental status changes ranging from agitation to coma. Although there are no human data pertinent to such an interaction with REMERON™, it is recommended that REMERON™ not be used in combination with an MAOI, or within 14 days of initiating or discontinuing therapy with an MAOI.

PRECAUTIONS

General

Somnolence

In U.S. controlled studies, somnolence was reported in 56% ~~54%~~ of patients treated with REMERON™ (mirtazapine), compared to 18% for placebo and 60% for amitriptyline. In a pooled analysis of all premarketing US studies, ~~in these studies,~~

(H
O✓)(H
O✓)

• This number is incorrect. Please see Table 1.

somnolence resulted in discontinuation for 16-8% 10.4% of REMERON™ treated patients, compared to 2.5% 2.2% for placebo. Several patients treated with REMERON™ experienced motor vehicle accidents, which in two cases were attributed to the severe somnolent effects of REMERON™. It is unclear whether or not tolerance develops to the somnolent effects of REMERON™. Because of REMERON™'s potentially significant effects on impairment of performance, patients should be cautioned about engaging in activities requiring alertness until they have been able to assess the drug's effect on their own psychomotor performance (see Information for Patients).

Dizziness

In U. S. controlled studies, dizziness was reported in 7% of patients treated with REMERON™ (mirtazapine), compared to 3% for placebo and 14% for amitriptyline. It is unclear whether or not tolerance develops to the dizziness observed in association with the use of REMERON™. While the orthostatic hypotension observed in early clinical pharmacology trials with REMERON™ was not frequently observed in later clinical trials, the dizziness observed in association with mirtazapine use in these later trials was likely a manifestation of the same pharmacological basis for the orthostatic hypotension, i.e. probably antagonism. Thus, the prescriber should be aware that there is some risk of postural hypotension in association with mirtazapine use. REMERON™ 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

- The Division had requested that AEs data be presented using the U.S. short-term placebo controlled studies. We believe, for consistency, that the same data base should be used for discontinuation rates due to these AEs. This is now consistent with the discontinuation table under the Adverse Reaction Section of the P.I.
- We believe that the Agency's decision to highlight the motor vehicle accidents (MVA) occurring in patients treated with REMERON™ is unjustified. All sedating drugs affect psychomotor performance and have the potential of causing MVAs. MVAs are not highlighted in any other sedated drugs labeling.

- The reports of dizziness and orthostatic hypotension are not necessarily the results of the same pharmacological mechanism. Dizziness may be associated with increased serotonergic activity. It is a common side effect with SSRIs and specific 5HT_{1A} agonists, eg., buspirone and gepirone (Reference #5). REMERON™ potentiates serotonergic activity indirectly through 5HT_{1A}, and thus dizziness may be a manifestation of that action.
- Caution about orthostatic hypotension is provided under "Use in patients with concomitant illness".

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antihypertensive medication):

Increased Appetite/Weight Gain Altered Appetite and Weight

In U.S. controlled studies, appetite increase was reported in 17% of patients treated with REMERON™ (mirtazapine), compared to 2% for placebo and 6% for amitriptyline. In these same trials, weight gain of $\geq 7\%$ of body weight was reported in 7.5% of patients treated with mirtazapine, compared to 0% for placebo and 5.9% for amitriptyline. In a pooled analysis of premarketing US studies, in these studies, weight gain resulted in discontinuation for 8.2% 0.9% of mirtazapine treated patients, compared to 0.3% for placebo.

Cholesterol/Triglycerides

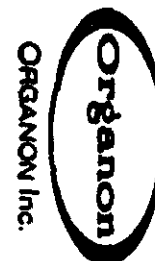
In U.S. controlled studies, nonfasting cholesterol increases to $\geq 20\%$ above the upper limits of normal were observed in 15% of patients treated with REMERON™ (mirtazapine), compared to 7% for placebo and 8% for amitriptyline. In these same studies, nonfasting triglyceride increases to ≥ 500 mg/dL were observed in 6% of patients treated with mirtazapine, compared to 3% for placebo and 3% for amitriptyline.

Transaminase Elevations

Clinically significant ALT (SGPT) elevations (≥ 3 times the upper

- Consistency for Headings with other antidepressants, e.g. Prozac, Wellbutrin.

- The Division had requested that all AEs data be presented using the short-term 6-week placebo controlled studies. We believe, for consistency, the same data base should be used for discontinuation rates due to AEs. The pooled analysis selected here includes long-term (greater than 1 year) open labeled treatment with REMERON™. The 8.2% discontinuation rate for REMERON™ reflects that duration, whereas the rate of 0.3% for placebo reflects only the short-term 6-week treatment.



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limit of the normal range) were observed in 2.0% (8/424) of patients exposed to REMERON™ in a pool of short-term US controlled trials, compared to 0.3% (1/328) of placebo patients and 2.0% (3181) of amitriptyline patients. Most of these patients with ALT increases did not develop signs or symptoms associated with compromised liver function. While some patients were discontinued for the ALT increases, in other cases, the enzyme levels returned to normal despite continued REMERON™ (mirtazapine) treatment. Mirtazapine should be used with caution in patients with impaired hepatic function (see Pharmacokinetics Section of Clinical Pharmacology, and Dosage and Administration).

Activation of Mania/Hypomania

Mania/hypomania occurred in approximately 0.2% (3/1,299 patients) of REMERON™ (mirtazapine) treated patients in U. S. studies. Although the incidence of mania/hypomania was very low during treatment with mirtazapine, it should be used carefully in patients with a history of mania/hypomania.

Seizures

In pre-marketing clinical trials only one seizure was reported among the 2,796 U.S. and non-U.S. patients treated with REMERON™ (mirtazapine). However, no controlled studies have been carried out in patients with a history of seizures. Therefore, care should be exercised when mirtazapine is used in these patients.

Suicide

Suicidal ideation is inherent in depression and may persist until significant remission occurs. As with any patient receiving antidepressants, high-risk patients should be closely supervised during initial drug therapy. Prescriptions of REMERON™ (mirtazapine) should be written for the smallest quantity consistent with good patient management, in order to reduce the risk of overdose.

Use in patients with concomitant illness

Clinical experience with REMERON™ (mirtazapine) 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.

Mirtazapine 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. Mirtazapine was not associated with clinically significant ECG abnormalities in U.S. and non-U.S. placebo controlled trials. Mirtazapine 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. While postural blood pressure changes were not noted in later clinical trials, dizziness was observed in these trials, and was likely a manifestation of the same pathophysiological process. Consequently, caution is recommended in treating patients who are vulnerable to changes in blood pressure (see Dizziness above). REMERON™ should be

- It should be noted that orthostatic hypotension was only observed in ~1% of Remeron patients.
- Dizziness and orthostatic hypotension are not necessarily of the same pharmacologic effect. Dizziness may be associated with increased serotonergic activity, as discussed on page 10.

need, with caution in patients with known cardiovascular or cerebral vascular 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).

OK

Mirtazapine clearance is decreased in patients with moderate (glomerular filtration rate (GFR) - 11-39 mL/min/1.73 m²) and severe (GFR < 10 mL/min/1.73 m²) renal impairment, and also in patients with hepatic impairment (See Pharmacokinetic Subsection of CLINICAL PHARMACOLOGY). Caution is indicated in administering REMERON™ to such patients (see DOSAGE AND ADMINISTRATION).

Information for patients

Physicians are advised to discuss the following issues with patients for whom they prescribe REMERON™:

Agranulocytosis

Patients who are to receive REMERON™ (mirtazapine) should be warned about the risk of developing agranulocytosis. Patients should be advised to report immediately the appearance of lethargy, weakness, fever, sore throat, malaise, contact their physician if they experience any indication of infection such as fever, chills, sore throat, mucous membrane ulceration or other possible signs of infection. Particular attention should be paid to any flu-like complaints or other symptoms that might suggest infection.

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- Inclusion of general terms like lethargy, weakness and malaise may cause undue concerns to patients and over-reporting to physicians. The proposed statement accurately describes the range of symptoms which may be consequences of neutropenia. It is also consistent with other labeling, eg, Ticlid and Tegretol.

Interference with Cognitive and Motor Performance

REMERON™ (mirtazapine) may impair judgement, thinking, and particularly, motor skills, because of its prominent sedative effect. The drowsiness associated with mirtazapine use may impair a patient's ability to drive, use machines or perform tasks that require alertness. Thus, patients should be cautioned about engaging in hazardous activities until they are reasonably certain that REMERON™ therapy does not adversely affect their ability to engage in such activities.

Completing Course of Therapy

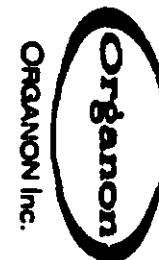
While patients may notice improvement with REMERON™ (mirtazapine) therapy in 1 to 4 weeks, they should be advised to continue therapy as directed.

Concomitant medication

Patients should be advised to inform their physicians if they are taking, or intent to take, any prescription or over-the-counter drugs since there is a potential for REMERON™ (mirtazapine) to interact with other drugs.

Alcohol

The impairment of cognitive and motor skills produced by REMERON™ (mirtazapine) has been shown to be additive with those produced by alcohol. Accordingly, patients should be advised to avoid alcohol while taking mirtazapine.



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Pregnancy

Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during REMERON™ (mirtazapine) therapy.

Nursing

Patients should be advised to notify their physician if they are breast-feeding an infant.

Laboratory tests

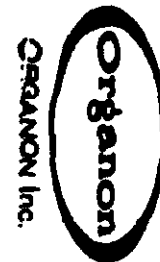
There are no routine laboratory tests recommended.

Drug Interactions

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

Drugs Affecting Hepatic Metabolism

The metabolism and pharmacokinetics of REMERON™ (mirtazapine) may be affected by the induction or inhibition of drug-metabolizing enzymes.



Drugs that are Metabolized by and/or Inhibit Cytochrome P450 Enzymes

Many drugs are metabolized by and/or inhibit various cytochrome P450 enzymes, e.g. 2D6, 1A2, 3A4, etc. Preliminary *in vitro* studies have shown that REMERON™ (mirtazapine) is a substrate for several of these enzymes, including primarily 2D6 and 1A2, and to much a lesser extent, 2C9 and 3A4. It is not known, however, whether or not *in vitro* study has shown that mirtazapine is a substantial inhibitor of any of these enzymes. This suggests that mirtazapine is likely to play a significant interactive role at the cytochrome P450 level with regards to the metabolism of co-administered drugs. Concomitant use of mirtazapine with most other drugs metabolized by cytochrome P450 enzymes has not been formally studied. Therefore, coadministration of mirtazapine with other drugs that are metabolized by these enzymes should be considered with care.

Alcohol

Concomitant administration of alcohol (equivalent to 60g) had a minimal effect on plasma levels of REMERON™ (15mg) in 6 healthy male subjects. However, the impairment of cognitive and motor skills produced by REMERON™ were shown to be additive with those produced by alcohol. Accordingly patients should be advised to avoid alcohol while taking REMERON™.

Diazepam

Concomitant administration of diazepam (15mg) had a minimal effect on plasma levels of mirtazapine (15mg) in 12 healthy subjects. However, the impairment of motor skills produced by REMERON™ has been shown to be additive with those caused by diazepam. Accordingly, patients should be advised to avoid

- Talk to
Sofia*
- Please refer to TNO report V95.648 provided as a response to FDA Biopharmaceutics request No. 1 in the Approvable letter (See Attachment 5 of the submission: Bogaards JJP, Haenen GRMM. The inhibition of the human cytochrome P450 enzymes CYP1A2, CYP2D6, and CYP3A by Org 3770 in human liver microsomes.)

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diazepam and other similar drugs while taking REMERON™.

Carcinogenesis, Mutagenesis, Impairment of Fertility

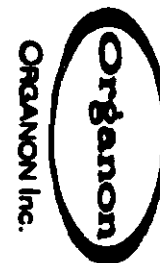
Carcinogenicity studies were conducted with REMERON™ (mirtazapine) given in the diet at doses of 2, 20, and 200 mg/kg/day to mice and 2, 20, and 60 mg/kg/day to rats. The highest doses used are approximately 20 and 12 times the maxim recommended human dose (MRHD) of 45 mg/day on a mg/m² basis in mice and rats, respectively. There was an increased incidence of hepatocellular adenoma and carcinoma in male mice at the high dose. In rats, there was an increase in hepatocellular adenoma in females at the mid and high doses and in hepatocellular tumors and thyroid follicular adenoma/cystadenoma and carcinoma in males at the high dose. The data suggests that the above effects could possibly be mediated by non-genotoxic mechanisms, the relevance of which to humans is not known.

The doses used in the mouse study may not have been high enough to fully characterize the carcinogenic potential of REMERON™.

Mutagenesis

REMERON™ was not mutagenic in the following ~~in vitro~~ ^{in vivo} clastogenic and ~~in vitro~~ ^{in vivo} general DNA damage as determined in several ~~genotoxicity tests~~: an Ames test and ~~in vitro~~ ^{in vivo} gene mutation assay in Chinese hamster V 79 cells. It was not clastogenic in an ~~in vitro~~ ^{in vivo} sister chromatic exchange assay in cultured rabbit lymphocytes or in an ~~in vitro~~ ^{in vivo} rat ~~bone marrow~~ micronucleus test.

- The information is incorrect. Sister chromatic exchange assay is not a clastogenicity test. It is a test that detects general DNA damage.



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~~in rats and~~ It was not genotoxic in an in vitro unscheduled DNA synthesis assay in HeLa cells. (201)

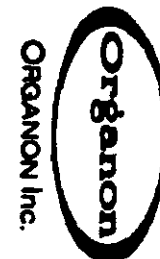
Impairment of Fertility

In a fertility study rats, REMERON™ was given at doses up to 20 times the maximum recommended human dose (MRHD) on a mg/m² basis. Mating and conception were not affected by the drug, but estrous cycling was disrupted at doses that were 3 or more times the MRHD and pre-implantation losses occurred at 20 times the MRHD.

Pregnancy

Teratogenic Effects - Pregnancy Category C

Reproduction studies in pregnant rats and rabbits at doses up to 20 and 17 times maximum recommended human dose (MRHD) on a mg/m² basis, respectively, have revealed no evidence of teratogenic effects. However, in rats, there was an increase in post-implantation losses in dams treated with REMERON™ (mirtazapine). There was an increase in pup deaths during the first 3 days of lactation and a decrease in pup birth weights. The cause of those deaths is not known. The effects occurred at doses that were 20 times the MRHD, but not at 3 times the MRHD, on a mg/m² basis. There are no adequate and well controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should not be used during pregnancy only if clearly needed.



Nursing Mothers

It is not known whether mirtazapine is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when REMERON™ (mirtazapine) Tablets are administered to nursing women.

Pediatric Use

Safety and effectiveness in children have not been established.

Geriatric Use

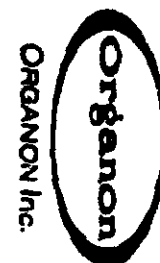
Approximately 190 elderly individuals (≥65 years of age) participated in clinical studies with REMERON™. No unusual adverse age-related phenomena were identified in this group. Pharmacokinetic studies revealed a decreased clearance in the elderly. Caution is indicated in administering REMERON™ to elderly patients (see Clinical Pharmacology and Dosage and Administration).

ADVERSE REACTIONS

Associated with discontinuation of treatment

Approximately 28 ~~16~~ percent of the ~~1229~~ ~~453~~ patients who received REMERON™ in US ~~6-week controlled~~ premarketing clinical trials discontinued treatment to an adverse experience. For short-term US placebo-controlled trial, The most common events (≥1%) associated with discontinuation and considered to be drug related (i.e., those events associated with dropout at a rate at least twice that of placebo) included:

- Consistent with the Division's request, AEs are presented for placebo controlled trials to assess the relative incidence of an adverse event against placebo. Discontinuation data should be similarly presented. The larger discontinuation rate in all U.S. studies is due to the long duration of treatment in an open-labeled long term study (up to 2½ years). This is noted in the Medical Reviewer's briefing document to the Advisory Committee, page 59.



Common Adverse Events Associated with Discontinuation of Treatment in 6-Week US REMERON™ Trials		
Adverse Events	Percentage of Patients Discontinuing with Adverse Event	
	REMERON™ (n=453)	Placebo (n=361)
Somnolence	10.4%	2.2%
Nausea	1.5%	0%

Commonly Observed Adverse Events in US Controlled Clinical Trials

The most commonly observed adverse events associated with the use of REMERON™ (incidence of 5% or greater) and not observed at an equivalent incidence among placebo-treated patients (REMERON™ incidence at least twice that for placebo) were: somnolence, increased appetite, weight gain and dizziness (10)

- Identification of most common AEs is sufficient here. Incidence rate is provided immediately in the 1% incidence table that follows. This format is consistent with other approved antidepressants' P.I.

Common Treatment-Emergent Adverse Events Associated with the Use of REMERON™ in 6-Week US Trials		
Adverse Event	Percentage of Patients Reporting Adverse Event	
	REMERON™ (n=453)	Placebo (n=361)
Somnolence	54%	18%
Increased Appetite	17%	2%
Weight Gain	12%	2%
Dizziness	7%	3%

(40)

Adverse Events Occurring at an Incidence of 1% or More Among REMERON™ Treated Patients

The table that follows enumerates adverse events that occurred at an incidence of 1% or more, and were more frequent than in the placebo group, among REMERON™-treated patients who participated in placebo-controlled trials in which patients were dosed in a range of 5 to 60 mg/day, seven, 6-week, placebo-controlled US studies in which patients were dosed with REMERON™ in a range of 5-35 mg/day. This table shows the percentage of patients in each group who at least one episode of an event at sometime during their treatment. Reported adverse

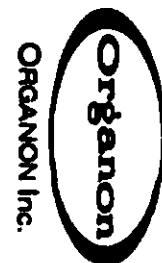
(14)

- This information is incorrect. The 1% incidence table includes all 8 placebo controlled short-term U.S. trials, including the dose response study up to 60 mg/day.

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events were classified using a standard COSTART-based dictionary terminology.

The prescriber should be aware that these figures cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristic and other factors differ from those which prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other investigations involving different treatments, uses and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and non-drug factors to the side effect incidence rate in the population studies.



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• The table has been changed as requested by FDA.

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TABLE 2
INCIDENCE OF ADVERSE CLINICAL EXPERIENCES
(≥ 1%)

IN SHORT-TERM U.S. CONTROLLED STUDIES

Body System Adverse Clinical Experience	Oxy 3770 (N=453)	Placebo (N=361)	Amisulpyrine (N=193)	Triazolone (N=49)
Body as a Whole	117 (25.8%)	98 (27.1%)	50 (26.1%)	25 (51.0%)
Headache	50 (11.0%) 11%	57 (15.8%) 16%	30 (15.5%)	10 (20.4%)
Asthma	34 (7.5%) 8%	17 (4.7%) 5%	21 (10.9%)	6 (12.2%)
Flu Syndrome	22 (4.9%) 5%	9 (2.5%) 3%	8 (4.1%)	5 (10.2%)
Back Pain	9 (2.0%) 2%	3 (0.8%) 1%	1 (0.5%)	3 (6.1%)
Infection	6 (1.3%) 1%	8 (2.2%) 2%	2 (1.0%)	2 (4.1%)
Pain	6 (1.3%) 1%	6 (1.7%) 2%	1 (0.5%)	2 (4.1%)
Chest Pain	5 (1.1%) 1%	4 (1.1%) 1%	1 (0.5%)	2 (4.1%)
Cardiovascular System	26 (5.7%)	24 (6.6%)	32 (16.6%)	14 (28.6%)
Palpitation	9 (2.0%) 2%	8 (2.2%) 2%	7 (3.6%)	6 (12.2%)
Tachycardia	5 (1.1%) 1%	4 (1.1%) 1%	11 (5.7%)	6 (12.2%)

TABLE 2
INCIDENCE OF ADVERSE CLINICAL EXPERIENCES
(≥1%)
IN SHORT-TERM U.S. CONTROLLED STUDIES

Body System Adverse Clinical Experience	Org 3770 (N=453)	Placebo (N=361)	Amitriptyline (N=193)	Flazodone (N=49)
Postural Hypotension	5 (1.1%) 1%	2 (0.6%) 1%	10 (5.2%)	1 (2.0%)
Digestive System	307 (67.7%)	100 (27.9%)	165 (85.5%)	35 (71.4%)
Dry Mouth	112 (24.7%) 25%	54 (15.0%) 15%	156 (80.8%)	30 (61.2%)
Increased Appetite	76 (16.8%) 17%	7 (1.9%) 2%	12 (6.2%)	3 (6.1%)
Constipation	57 (12.6%) 13%	24 (6.6%) 7%	50 (25.9%)	12 (24.5%)
Nausea	19 (4.2%) 4%	19 (5.3%) 5%	9 (4.7%)	7 (14.3%)
Dyspnea	11 (2.4%) 2%	9 (2.5%) 2%	40 (20.7%)	6 (12.2%)
Diarrhea	11 (2.4%) 2%	16 (4.4%) 4%	3 (1.6%)	7 (14.3%)
Flatulence	6 (1.3%) 1%	4 (1.1%) 1%	3 (1.6%)	5 (10.2%)
Hemic and Lymphatic System	5 (1.1%)	2 (0.6%)	0	0
Metabolic and Nutritional Disorders	71 (15.7%)	13 (3.6%)	16 (8.3%)	0 (0.0%)
Weight Gain	54 (11.9%) 12%	6 (1.7%) 2%	13 (6.7%)	2 (4.1%)

TABLE 2
INCIDENCE OF ADVERSE CLINICAL EXPERIENCES
(≥1%)
IN SHORT-TERM U.S. CONTROLLED STUDIES

Body System Adverse Clinical Experience	Org 3770 (N=453)	Placebo (N=361)	Amitriptyline (N=193)	Trimidone (N=49)
Peripheral Edema	11 (2.4%)	4 (1.1%)	2 (1.0%)	1 (2.0%)
Edema	6 (1.3%)	1 (0.3%)	3 (1.6%)	2 (4.1%)
Musculoskeletal System	15 (3.3%)	11 (3.0%)	6 (3.1%)	6 (12.2%)
Myalgia	9 (2.0%)	3 (0.8%)	4 (2.1%)	0
Nervous System	200 (63.6%)	117 (32.4%)	154 (79.8%)	36 (73.5%)
Somnolence	243 (53.6%)	65 (18.0%)	115 (59.6%)	27 (55.1%)
Dizziness	33 (7.3%)	12 (3.3%)	27 (14.0%)	13 (26.5%)
Abnormal Dreams	19 (4.2%)	5 (1.4%)	3 (1.6%)	3 (6.1%)
Insomnia	17 (3.8%)	21 (5.8%)	2 (1.0%)	0
Nervousness	20 (4.4%)	15 (4.2%)	20 (10.4%)	9 (18.4%)
Thinking Abnormal	15 (3.3%)	4 (1.1%)	0 (0.0%)	4 (8.2%)
Tremor	7 (1.5%)	2 (0.6%)	22 (11.4%)	3 (6.1%)
Confusion	9 (2.0%)	1 (0.3%)	12 (6.2%)	2 (4.1%)

TABLE 2
INCIDENCE OF ADVERSE CLINICAL EXPERIENCES
(≥1%)

IN SHOF T-TERM U.S. CONTROLLED STUDIES

Body System Adverse Clinical Experience	Org 3770 (N=453)	Placebo (N=361)	Amisulpyline (N=193)	Frazadone (N=49)
Libido Decreased	6 (1.3%)	4 (1.1%)	6 (3.1%)	2 (4.1%)
Hypertonia	6 (1.3%)	4 (1.1%)	0	1 (2.0%)
Respiratory System	26 (5.7%)	21 (5.8%)	14 (7.3%)	10 (30.4%)
Pharyngitis	0 (0.0%)	6 (1.7%)	5 (2.6%)	2 (4.1%)
Dyspnea	5 (1.1%)	1 (0.3%)	3 (1.6%)	2 (4.1%)
Rhinitis	6 (1.3%)	5 (1.4%)	4 (2.1%)	5 (10.2%)
Skin and Appendages	10 (4.0%)	23 (6.4%)	10 (9.3%)	6 (12.2%)
Sweating	5 (1.1%)	3 (0.8%)	6 (3.1%)	0
Special Senses	33 (7.3%)	22 (6.1%)	49 (25.4%)	19 (38.8%)
Urvial System	25 (5.5%)	19 (5.3%)	23 (11.9%)	6 (12.2%)
Urinary Frequency	0 (0.0%)	5 (1.4%)	1 (0.5%)	2 (4.1%)
Adipsia	11 (2.4%)	6 (1.7%)	29 (15.0%)	5 (10.2%)
Tinnitus	6 (1.3%)	3 (0.8%)	4 (2.1%)	1 (2.0%)

TABLE 2
INCIDENCE OF ADVERSE CLINICAL EXPERIENCES
(≥1%)
IN SHORT-TERM U.S. CONTROLLED STUDIES

Body System Adverse Clinical Experience	Org 3770 (N=453)	Placebo (N=361)	Amitriptyline (N=193)	Trazodone (N=49)
✓ Taste Perversion	6 (1.3%) 1%	3 (0.8%) 1%	14 (7.3%)	3 (6.1%)
Miscellaneous	4 (0.9%)	8 (2.2%)	3 (1.6%)	1 (2.0%)
Total	377 (83.2%)	234 (64.8%)	185 (95.9%)	48 (98.0%)

The following ~~adverse~~ events were seen more frequently in REMERON™ patients in the non-U.S. placebo-controlled studies than in the short-term U.S. placebo-controlled studies: Asthenia; pain; chest pain; back pain; palpitation; postural hypotension; dyspepsia; flatulence; nausea; dry mouth; constipation; myalgia; libido decreased; abnormal dreams; insomnia; nervousness; thinking abnormal; dyspnea; sweating; tinnitus; taste perversion; urinary frequency; tremor.

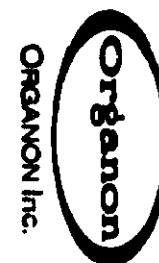
ECG Changes

In an analysis of ECGs obtained in U.S. placebo-controlled clinical trials, REMERON™ and placebo-treated patients had a similar incidence of abnormal changes from baseline at 6-8 weeks of approximately 3%. The abnormalities were generally not considered clinically significant.

Other Adverse Events Observed During the Premarketing Evaluation of REMERON™

During its premarketing assessment, multiple doses of REMERON™ (mirtazapine) were administered to 2796 patients in clinical studies. The conditions and duration of exposure to

✓ = go into footnote



mirtazapine varied greatly, and included (in overlapping categories) open and double-blind studies, uncontrolled and controlled studies, inpatient and outpatient studies, fixed dose and titration studies. Untoward events associated with this exposure were recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of untoward events into a smaller number of standardized event categories.

In the tabulations that follow, reported adverse events were classified using a standard COSTART-based dictionary terminology. The frequencies presented, therefore, represent the proportion of the 2796 patients exposed to multiple doses of REMERON™ who experienced an event of the type cited on at least one occasion while receiving REMERON™. All reported events are included except those already listed in the previous table, those adverse experiences subsumed under COSTART terms that are either overly general or excessively specific so as to be uninformative, and those events for which a drug cause was very remote.

It is important to emphasize that, although the events reported occurred during treatment with REMERON™, they were not necessarily caused by it.

Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse events are those occurring on one or more occasions in at least 1/100 patients; infrequent adverse events are those occurring in 1/100 to 1/1000 patients; rare events are those

occurring in fewer than 1/1000 patients. Only those events not already listed in Table 2 appear in this listing. Events of major clinical importance are also described in the WARNINGS and PRECAUTIONS sections.

Body as a whole: frequent: malaise, abdominal pain, abdominal syndrome acute; *infrequent:* chills, fever, face edema, ulcer, photosensitivity reaction, neck rigidity, neck pain, abdomen enlarged; *rare:* cellulitis, chest pain substernal.

Cardiovascular System: *frequent:* hypertension, vasodilation; *infrequent:* angina pectoris, myocardial infarction, bradycardia, ventricular extrasystoles, syncope, migraine, hypotension; *rare:* atrial arrhythmia, bigeminy, vascular headache, pulmonary embolus, cerebral ischemia, cardiomegaly, phlebitis, left heart failure.

Digestive System: *frequent:* vomiting, anorexia; *infrequent:* eructation, glossitis, cholecystitis, cholecystitis, nausea and vomiting, gag hemorrhage, stomatitis, colitis, liver function test abnormal; *rare:* tongue discoloration, ulcerative stomatitis, salivary gland enlargement, increased salivation, intestinal obstruction, pancreatitis, aphthous stomatitis, cirrhosis of liver, gastritis, gastroenteritis, oral moniliasis, tongue edema.

Endocrine System: *rare:* goiter, hypothyroidism.

Hemic and Lymphatic System: *rare:* lymphadenopathy, leukopenia, patachia, anemia, thrombocytopenia, lymphocytosis, pancytopenia.

Metabolic and Nutritional Disorders: *frequent:* thirst; *infrequent:* dehydration, weight loss, *rare:* gout, SGOT increased, healing abnormal, acid phosphatase increased, SGPT increased, diabetes mellitus.

Musculoskeletal System: *frequent:* myasthenia, arthralgia; *infrequent:* arthritis, tenosynovitis; *rare:* pathological fracture, osteoporosis fracture, bone pain, myositis, tendon rupture, arthrosis, bursitis.

Nervous System: *frequent:* hypesthesia, apathy, depression, hypokinesia, vertigo, twitching, agitation anxiety, amnesia, hyperkinesia, paresthesia; *infrequent:* ataxia, delirium, delusions, depersonalization, dyskinesia, extrapyramidal syndrome, libido increased, coordination abnormal, dysarthria, hallucinations, manic reaction, neurosis, dystonia, hostility, reflexes increased, emotional lability, euphoria, paranoid reaction; *rare:* aphasia, nystagmus, akathisia, stupor, dementia, diplopia, drug dependence, paralysis, grand malconvulsion, hypotonia, myoclonus, psychotic depression, withdrawal syndrome.

Respiratory Systems: *frequent:* cough increased, sinusitis; *infrequent:* epistaxis, bronchitis, asthma, pneumonia; *rare:* asphyxia, laryngitis, pneumothorax, hiccup.

Skin and Appendages: *frequent:* pruritus, rash; *infrequent:* acne, exfoliative dermatitis, dry skin, herpes simplex, alopecia; *rare:* urticaria, herpes zoster, skin hypertrophy, seborrhea, skin ulcer.

Special Senses: *infrequent:* eye pain, abnormality of accommodation, conjunctivitis, deafness, keratoconjunctivitis, lacrimation disorder, glaucoma, hyperacusis, ear pain; *rare:*

blepharitis, partial transitory deafness, otitis media, taste loss, parosmia.

Urogenital System: frequent: urinary tract infection; infrequent: kidney calculus, cystitis, dysuria, urinary incontinence, urinary retention, vaginitis, hematuria, breast pain, amenorrhea, dysmenorrhea, leukorrhea, impotence. rare: polyuria, urethritis, metrorrhagia, menorrhagia, abnormal ejaculation, breast engorgement, breast enlargement, urinary urgency.

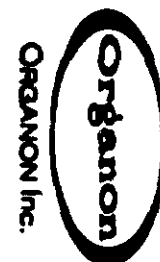
DRUG ABUSE AND DEPENDENCE

Controlled Substance Class

REMERON™ (mirtazapine) Tablets are not a controlled substance.

Physical and Psychologic Dependence

REMERON™ (mirtazapine) has not been systematically studied in animals or humans for its potential for abuse, tolerance or physical dependence. While the clinical trials did not reveal any tendency for any drug-seeking behavior, these observations were not systematic and it is not possible to predict on the basis of this limited experience the extent to which a CNS-active drug will be misused, diverted and/or abused once marketed. Consequently, patients should be evaluated carefully for history of drug abuse, and such patients should be observed closely for signs of mirtazapine misuse or abuse (e.g., development of tolerance, incrementations of dose, drug-seeking behavior).



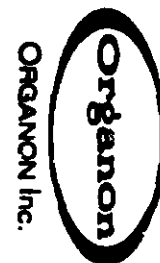
OVERDOSAGE

Human Experience

There is very limited experience with REMERON™ (mirtazapine) overdose. In premarketing clinical studies, there were nine reports of mirtazapine overdose alone or in combination with other pharmacological agents. The only drug overdose death reported while taking REMERON™ (mirtazapine) Tablets was in combination with amitriptyline and chlorprohixene in a non-U.S. clinical study. Based on plasma levels, the REMERON™ dose taken was 30-45 mg, while plasma levels of amitriptyline and chlorprohixene were found to be at toxic levels. All other premarketing overdose cases resulted in full recovery. Signs and symptoms reported in association with overdose included disorientation, drowsiness, impaired memory, and tachycardia. There were no reports of ECG abnormalities, coma or convulsions following overdose with REMERON™ alone.

Overdose Management

Treatment should consist of those general measures employed in the management of overdose with any antidepressant. There are no specific antidotes for REMERON™. If the patient is unconscious, establish and maintain an airway to ensure adequate oxygenation and ventilation. Gastric evacuation either by the induction of emesis or lavage or both should be considered. Activated charcoal should also be considered in treatment of overdose. Cardiac and vital signs monitoring is recommended along with general symptomatic and supportive measures.



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In managing overdose, consider the possibility of multiple-drug involvement. The physician should consider contacting a poison control center for additional information on the treatment of any overdose.

DOSAGE AND ADMINISTRATION

Initial Treatment

The recommended starting dose for REMERON™ (mirtazapine) is 15 mg/day, administered in a single dose, preferably in the evening prior to sleep. In the controlled clinical trials establishing the antidepressant efficacy of REMERON™, the effective dose range was generally 15-45 mg/day. While the relationship between dose and antidepressant response for REMERON™ has not been adequately explored, patients not responding to the initial 15 mg dose may benefit from dose increases up to a maximum of 45 mg/day. REMERON™ has an elimination half-life of approximately 20-40 hours, therefore, dose changes should not be made at intervals of less than one to two weeks in order to allow sufficient time for evaluation of the therapeutic response to a given dose.

Elderly and Patients with Renal or Hepatic Impairment

In elderly patients, clearance is reduced but there is no age related increase in adverse events. Remeron™ should be dosed with care in the elderly patients. In elderly patients, in patients with moderate to severe renal impairment, and in patients with hepatic impairment, REMERON™'s clearance is reduced by about 30%,

- *There is no clinical evidence to suggest that elderly patients cannot tolerate up to 45 mg. Therefore, this option should remain open and a cautionary statement should be adequate.*

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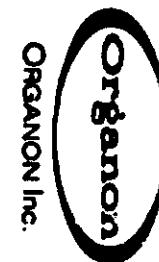
and a dose of 30 mg should not be exceeded in these patients. (See Pharmacokinetics Subsection of CLINICAL PHARMACOLOGY).

Maintenance/Extended Treatment

There is no body of evidence available from controlled trials to indicate how long the depressed patient should be treated with REMERON™. It is generally agreed, however, that pharmacological treatment for acute episodes of depression should continue for up to six months or longer. Whether the dose of antidepressant needed to induce remission is identical to the dose needed to maintain euthymia is unknown.

Switching Patients to or from a Monoamine Oxidase Inhibitor

At least 14 days should elapse between discontinuation of an MAOI and initiation of therapy with REMERON™. In addition, at least 14 days should be allowed after stopping REMERON™ before starting an MAOI.



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HOW SUPPLIED

REMERON™ (mirtazapine) Tablets are supplied as:

15 mg Tablets - oval, scored, yellow, coated, with "Organon" embossed on one side and "TZ3" on the other side.

Bottles of 30	NDC # 0052-0105-30
Bottles of 100	NDC # 0052-0105-91
Bottles of 500	NDC # 0052-0105-95
Unit Dose, Box of 100	NDC # 0052-0105-90*

30 mg Tablets - oval, scored, red-brown, coated, with "Organon" embossed on one side and "TZ5" on the other side.

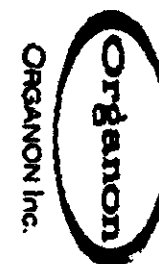
Bottles of 30	NDC # 0052-0107-30
Bottles of 100	NDC # 0052-0107-91
Bottles of 500	NDC # 0052-0107-95
Unit Dose, Box of 100	NDC # 0052-0107-90*

*Unit dose packs are provided as a blisterpack with 10 strips, each of which contain 10 tablets.

Store at controlled Room Temperature
20°-25°C (68°-77°F)

Dispense in a tight, light resistant container.

Caution: Federal law prohibits dispensing without prescription.



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5-10-96
submission

ATTACHMENT 4

Final Labeling Proposal

0217

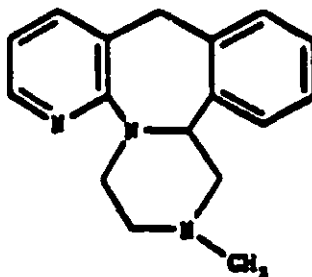
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REMERON™

(mirtazapine) Tablets

DESCRIPTION

REMERON™ (mirtazapine) is an antidepressant for oral administration. It has a tetracyclic chemical structure unrelated to selective serotonin reuptake inhibitors, tricyclics or monoamine oxidase inhibitors (MAOI). Mirtazapine belongs to the piperazino-azepine group of compounds. It is designated 1,2,3,4,10,14b-hexahydro-2-methylpyrazino [2,1-a] pyrido [2,3-c] benzazepine and has the empirical formula of $C_{17}H_{19}N_3$. Its molecular weight is 265.36. The structural formula is the following and it is the racemic mixture:



Mirtazapine is a white to creamy white crystalline powder which is slightly soluble in water.

REMERON™ is supplied for oral administration as scored film-coated tablets containing 15 or 30 mg of mirtazapine. Each tablet also contains corn starch, hydroxypropyl cellulose, magnesium stearate, colloidal silicon dioxide, lactose, and other inactive ingredients.

CLINICAL PHARMACOLOGY

Pharmacodynamics

The mechanism of action of REMERON™ (mirtazapine), as with other antidepressants, is unknown.

Evidence gathered in preclinical studies suggests that mirtazapine enhances central noradrenergic and serotonergic activity. These studies have shown that mirtazapine acts as an antagonist at central presynaptic α_2 adrenergic inhibitory autoreceptors and heteroreceptors, an action that is postulated to result in an increase in central noradrenergic and serotonergic activity.



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Mirtazapine is a potent antagonist of 5-HT₂ and 5-HT₃ receptors. Mirtazapine has no significant affinity for the 5-HT_{1A} and 5-HT_{1B} receptors.

Mirtazapine is a potent antagonist of histamine (H₁) receptors, a property that may explain its prominent sedative effects.

Mirtazapine is a moderate peripheral α_1 adrenergic antagonist, a property that may explain the occasional orthostatic hypotension reported in association with its use.

Mirtazapine is a moderate antagonist at muscarinic receptors, a property that may explain the relatively low incidence of anticholinergic side effects associated with its use.

Pharmacokinetics

REMERON™ (mirtazapine) is rapidly and completely absorbed following oral administration and has a half-life of about 20-40 hours. Peak plasma concentrations are reached within about 2 hours following an oral dose. The presence of food in the stomach has a minimal effect on both the rate and extent of absorption and does not require a dosage adjustment.

Mirtazapine is extensively metabolized after oral administration. Major pathways of biotransformation are demethylation and hydroxylation followed by glucuronide conjugation. In-vitro data from human liver microsomes indicates that cytochrome 2D6 and 1A2 are involved in the formation of the 8-hydroxy metabolite of mirtazapine, whereas cytochrome 3A is considered to be responsible for the formation of the N-desmethyl and N-oxide metabolite. Mirtazapine has an absolute bioavailability of about 50%. It is eliminated predominantly via urine (75%) with 15% in feces. Several unconjugated metabolites possess pharmacological activity but are present in the plasma at very low levels. The (-) enantiomer has an elimination half-life that is approximately twice as long as the (+) enantiomer and therefore achieves plasma levels that are about three times as high as that of the (+) enantiomer.

Plasma levels are linearly related to dose over a dose range of 15 to 80 mg. The mean elimination half-life of mirtazapine after oral administration ranges from approximately 20-40 hours across age and gender subgroups, with females of all ages exhibiting significantly longer elimination half-lives than males (mean half-life of 37 hours for females vs 26 hours for males). Steady state plasma levels of mirtazapine are attained within 5 days, with about 50% accumulation (accumulation ratio = 1.5).

Mirtazapine is approximately 85% bound to plasma proteins over a concentration range of 0.01 to 10 µg/mL.

Population Subgroups

Liver Disease - Following a single 15 mg oral dose of mirtazapine, the oral clearance of mirtazapine was decreased by approximately 30% in hepatically impaired patients compared to subjects with

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normal hepatic function. Caution is indicated in administering REMERON™ to patients with compromised hepatic function (see Precautions and Dosage and Administration).

Renal Disease - Following a single 15 mg oral dose of mirtazapine, patients with moderate [glomerular filtration rate (GFR) = 11-39 mL/min/1.73 m²] and severe [GFR <10mL/min/1.73m²] renal impairment had reductions in mean oral clearance of mirtazapine of about 30% and 50%, respectively, compared to normal subjects. Caution is indicated in administering REMERON™ to patients with compromised renal function (see Precautions and Dosage and Administration).

Elderly Patients - Following oral administration of mirtazapine 20 mg/day for 7 days to subjects of varying ages (range, 25-74), oral clearance of mirtazapine was reduced in the elderly compared to the younger subjects. The differences were most striking in males, with a 40% lower clearance in elderly males compared to younger males, while the clearance in elderly females was only 10% lower compared to younger females. Caution is indicated in administering REMERON™ to elderly patients (see Precautions and Dosage and Administration).

Clinical Trials Showing Effectiveness

The efficacy of REMERON™ (mirtazapine) as a treatment for depression was established in four placebo-controlled, 6-week trials in adult outpatients meeting DSM-III criteria for major depression. Patients were titrated with mirtazapine from a dose range of 5 mg up to 35 mg/day. Overall, these studies demonstrated mirtazapine to be superior to placebo on at least three of the following four measures: 21-Item Hamilton Depression Rating Scale (HDRS) total score; HDRS Depressed Mood Item; CGI Severity score; and Montgomery and Asberg Depression Rating Scale (MADRS). Superiority of mirtazapine over placebo was also found for certain factors of the HDRS, including anxiety/somatization factor and sleep disturbance factor. The mean mirtazapine dose for patients who completed these four studies ranged from 21 to 32 mg/day. A fifth study of similar design utilized a higher dose (up to 50 mg) per day and also showed effectiveness.

Examination of age and gender subsets of the population did not reveal any differential responsiveness on the basis of these subgroupings.

INDICATIONS AND USAGE

REMERON™ (mirtazapine) Tablets are indicated for the treatment of depression.

The efficacy of REMERON™ in the treatment of depression was established in six week controlled trials of outpatients whose diagnoses corresponded most closely to the Diagnostic and Statistical Manual of Mental Disorders - 3rd edition (DSM-III) category of major depressive disorder (see CLINICAL PHARMACOLOGY).



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A major depressive episode (DSM-IV) implies a prominent and relatively persistent (nearly every day for at least 2 weeks) depressed or dysphoric mood that usually interferes with daily functioning, and includes at least five of the following nine symptoms: depressed mood, loss of interest in usual activities, significant change in weight and/or appetite, insomnia or hypersomnia, psychomotor agitation or retardation, increased fatigue, feelings of guilt or worthlessness, slowed thinking or impaired concentration, a suicide attempt or suicidal ideation.

The antidepressant effectiveness of REMERON™ (mirtazapine) in hospitalized depressed patients has not been adequately studied.

The effectiveness of REMERON™ in long-term use, that is, for more than 6 weeks, has not been systematically evaluated in controlled trials. Therefore, the physician who elects to use REMERON™ for extended periods should periodically evaluate the long-term usefulness of the drug for the individual patient.

CONTRAINDICATIONS

REMERON™ (mirtazapine) Tablets are contraindicated in patients with a known hypersensitivity to mirtazapine.

WARNINGS

Agranulocytosis

In premarketing clinical trials, two (one with Sjögren's Syndrome) out of 2,796 patients treated with REMERON™ (mirtazapine) Tablets developed agranulocytosis (absolute neutrophil count (ANC) $< 500/\text{mm}^3$ with associated signs and symptoms, e.g., fever, infection, etc.) and a third patient developed severe neutropenia (ANC $< 500/\text{mm}^3$ without any associated symptoms). For these three patients, onset of severe neutropenia was detected on days 9, 14, and 61, 9, and 14 of treatment, respectively. All three patients recovered after Remeron was stopped. These three cases yield a crude incidence of severe neutropenia (with or without associated infection) of approximately 1.1 per thousand patients exposed, with a very wide 95% confidence interval, i.e., 2.2 cases per 10,000 to 3.1 cases per 1000. If a patient develops a sore throat, fever, stomatitis or other signs of infection, along with a low WBC count, treatment with REMERON™ should be discontinued and the patient should be closely monitored.

MAO Inhibitors

In patients receiving other antidepressants in combination with a monoamine oxidase inhibitor (MAOI) and in patients who have recently discontinued an antidepressant drug and then are

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started on an MAOI, there have been reports of serious, and sometimes fatal, reactions, e.g., including nausea, vomiting, flushing, dizziness, tremor, myoclonus, rigidity, diaphoresis, hyperthermia, autonomic instability with rapid fluctuations of vital signs, seizures, and mental status changes ranging from agitation to coma. Although there are no human data pertinent to such an interaction with REMERON™, it is recommended that REMERON™ not be used in combination with an MAOI, or within 14 days of initiating or discontinuing therapy with an MAOI.

PRECAUTIONS

General

Somnolence

In U.S. controlled studies, somnolence was reported in 54% of patients treated with REMERON™ (mirtazapine), compared to 18% for placebo and 60% for amitriptyline. In these studies, somnolence resulted in discontinuation for 10.4% of REMERON™ treated patients, compared to 2.2% for placebo. It is unclear whether or not tolerance develops to the somnolent effects of REMERON™. Because of Remeron's potentially significant effects on impairment of performance, patients should be cautioned about engaging in activities requiring alertness until they have been able to assess the drug's effect on their own psychomotor performance (see Information for Patients).

Dizziness

In U. S. controlled studies, dizziness was reported in 7% of patients treated with REMERON™ (mirtazapine), compared to 3% for placebo and 14% for amitriptyline. It is unclear whether or not tolerance develops to the dizziness observed in association with the use of Remeron.

Increased Appetite/Weight Gain

In U.S. controlled studies, appetite increase was reported in 17% of patients treated with REMERON™ (mirtazapine), compared to 2% for placebo and 6% for amitriptyline. In these same trials, weight gain of $\geq 7\%$ of body weight was reported in 7.5% of patients treated with mirtazapine, compared to 0% for placebo and 5.9% for amitriptyline. In a pool of premarketing U.S. studies, including many patients for long-term, open label treatment, 8% of patients receiving REMERON™ discontinued for weight gain.

Cholesterol/Triglycerides

In U.S. controlled studies, nonfasting cholesterol increases to $\geq 20\%$ above the upper limits of normal were observed in 15% of patients treated with REMERON™ (mirtazapine), compared to 7% for placebo and 8% for amitriptyline. In these same studies, nonfasting triglyceride increases

to ≥ 500 mg/dL were observed in 6% of patients treated with mirtazapine, compared to 3% for placebo and 3% for amitriptyline.

Transaminase Elevations

Clinically significant ALT (SGPT) elevations (≥ 3 times the upper limit of the normal range) were observed in 2.0% (8/424) of patients exposed to REMERON™ in a pool of short-term US controlled trials, compared to 0.3% (1/328) of placebo patients and 2.0% (3/181) of amitriptyline patients. Most of these patients with ALT increases did not develop signs or symptoms associated with compromised liver function. While some patients were discontinued for the ALT increases, in other cases, the enzyme levels returned to normal despite continued REMERON™ (mirtazapine) treatment. Mirtazapine should be used with caution in patients with impaired hepatic function (see Pharmacokinetics section of Clinical Pharmacology, and Dosage and Administration).

Activation of Mania/Hypomania

Mania/hypomania occurred in approximately 0.2% (3/1,299 patients) of REMERON™ (mirtazapine) treated patients in U. S. studies. Although the incidence of mania/hypomania was very low during treatment with mirtazapine, it should be used carefully in patients with a history of mania/hypomania.

Seizures

In pre-marketing clinical trials only one seizure was reported among the 2,796 U.S. and non-U.S. patients treated with REMERON™ (mirtazapine). However, no controlled studies have been carried out in patients with a history of seizures. Therefore, care should be exercised when mirtazapine is used in these patients.

Suicide

Suicidal ideation is inherent in depression and may persist until significant remission occurs. As with any patient receiving antidepressants, high-risk patients should be closely supervised during initial drug therapy. Prescriptions of REMERON™ (mirtazapine) should be written for the smallest quantity consistent with good patient management, in order to reduce the risk of overdose.

Use in patients with concomitant illness

Clinical experience with REMERON™ (mirtazapine) 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.

Mirtazapine 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. Mirtazapine was not

associated with clinically significant ECG abnormalities in U.S. and non-U.S. placebo controlled trials. Mirtazapine 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™ 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).

Mirtazapine clearance is decreased in patients with moderate [glomerular filtration rate (GFR) = 11-39 mL/min/1.73 m²] and severe [GFR < 10 mL/min/1.73 m²] renal impairment, and also in patients with hepatic impairment (See Pharmacokinetic Subsection of CLINICAL PHARMACOLOGY). Caution is indicated in administering REMERON™ to such patients (see DOSAGE AND ADMINISTRATION).

Information for patients

Physicians are advised to discuss the following issues with patients for whom they prescribe REMERON™:

Agranulocytosis

Patients who are to receive REMERON™ (mirtazapine) should be warned about the risk of developing agranulocytosis. Patients should be advised to contact their physician if they experience any indication of infection such as, fever, chills, sore throat, mucous membrane ulceration or other possible signs of infection. Particular attention should be paid to any flu-like complaints or other symptoms that might suggest infection.

Interference with Cognitive and Motor Performance

REMERON™ (mirtazapine) may impair judgement, thinking, and particularly, motor skills, because of its prominent sedative effect. The drowsiness associated with mirtazapine use may impair a patient's ability to drive, use machines or perform tasks that require alertness. Thus, patients should be cautioned about engaging in hazardous activities until they are reasonably certain that REMERON™ therapy does not adversely affect their ability to engage in such activities.

Completing Course of Therapy

While patients may notice improvement with REMERON™ (mirtazapine) therapy in 1 to 4 weeks, they should be advised to continue therapy as directed.



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Concomitant medication

Patients should be advised to inform their physician if they are taking, or intend to take, any prescription or over-the-counter drugs since there is a potential for REMERON™ (mirtazapine) to interact with other drugs.

Alcohol

The impairment of cognitive and motor skills produced by REMERON™ (mirtazapine) has been shown to be additive with those produced by alcohol. Accordingly, patients should be advised to avoid alcohol while taking mirtazapine.

Pregnancy

Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during REMERON™ (mirtazapine) therapy.

Nursing

Patients should be advised to notify their physician if they are breast-feeding an infant.

Laboratory tests

There are no routine laboratory tests recommended.

Drug Interactions

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).

Drugs Affecting Hepatic Metabolism

The metabolism and pharmacokinetics of REMERON™ (mirtazapine) may be affected by the induction or inhibition of drug-metabolizing enzymes.

Drugs that are Metabolized by and/or Inhibit Cytochrome P450 Enzymes

Many drugs are metabolized by and/or inhibit various cytochrome P450 enzymes, e.g. 2D6, 1A2, 3A4, etc. In vitro studies have shown that REMERON™ (mirtazapine) is a substrate for several of these enzymes, including 2D6, 1A2, and 3A4. While in vitro studies have shown that mirtazapine is not a potent inhibitor of any of these enzymes, an indication that mirtazapine is not likely to have a clinically significant inhibitory effect on the metabolism of other drugs that are substrates for

these cytochrome P450 enzymes, the concomitant use of mirtazapine with most other drugs metabolized by these enzymes has not been formally studied. Consequently, it is not possible to make any definitive statements about the risks of coadministration of mirtazapine with such drugs.

Alcohol

Concomitant administration of alcohol (equivalent to 60g) had a minimal effect on plasma levels of REMERON™ (15mg) in 6 healthy male subjects. However, the impairment of cognitive and motor skills produced by REMERON™ were shown to be additive with those produced by alcohol. Accordingly, patients should be advised to avoid alcohol while taking REMERON™.

Diazepam

Concomitant administration of diazepam (15mg) had a minimal effect on plasma levels of mirtazapine (15mg) in 12 healthy subjects. However, the impairment of motor skills produced by REMERON™ has been shown to be additive with those caused by diazepam. Accordingly, patients should be advised to avoid diazepam and other similar drugs while taking REMERON™.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Carcinogenicity studies were conducted with REMERON™ (mirtazapine) given in the diet at doses of 2, 20, and 200 mg/kg/day to mice and 2, 20, and 60 mg/kg/day to rats. The highest doses used are approximately 20 and 12 times the maximum recommended human dose (MRHD) of 45 mg/day on a mg/m² basis in mice and rats, respectively. There was an increased incidence of hepatocellular adenoma and carcinoma in male mice at the high dose. In rats, there was an increase in hepatocellular adenoma in females at the mid and high doses and in hepatocellular tumors and thyroid follicular adenoma/cystadenoma and carcinoma in males at the high dose. The data suggests that the above effects could possibly be mediated by non-genotoxic mechanisms, the relevance of which to humans is not known.

The doses used in the mouse study may not have been high enough to fully characterize the carcinogenic potential of REMERON™.

Mutagenesis

REMERON™ was not mutagenic or clastogenic and did not induce general DNA damage as determined in several genotoxicity tests: Ames test, in vitro gene mutation assay in Chinese hamster V 79 cells, in vitro sister chromatid exchange assay in cultured rabbit lymphocytes, in vivo bone marrow micronucleus test in rats, and unscheduled DNA synthesis assay in HeLa cells.

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Impairment of Fertility

In a fertility study in rats, REMERON™ was given at doses up to 20 times the maximum recommended human dose (MRHD) on a mg/m² basis. Mating and conception were not affected by the drug, but estrous cycling was disrupted at doses that were 3 or more times the MRHD and pre-implantation losses occurred at 20 times the MRHD.

Pregnancy

Teratogenic Effects - Pregnancy Category C

Reproduction studies in pregnant rats and rabbits at doses up to 20 and 17 times the maximum recommended human dose (MRHD) on a mg/m² basis, respectively, have revealed no evidence of teratogenic effects. However, in rats, there was an increase in post-implantation losses in dams treated with REMERON™ (mirtazapine). There was an increase in pup deaths during the first 3 days of lactation and a decrease in pup birth weights. The cause of those deaths is not known. The effects occurred at doses that were 20 times the MRHD, but not at 3 times the MRHD, on a mg/m² basis. There are no adequate and well controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers

It is not known whether mirtazapine is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when REMERON™ (mirtazapine) Tablets are administered to nursing women.

Pediatric Use

Safety and effectiveness in children have not been established.

Geriatric Use

Approximately 190 elderly individuals (>65 years of age) participated in clinical studies with Remeron. No unusual adverse age-related phenomena were identified in this group. Pharmacokinetic studies revealed a decreased clearance in the elderly. Caution is indicated in administering REMERON™ to elderly patients (see Clinical Pharmacology and Dosage and Administration).

ADVERSE REACTIONS

Associated with discontinuation of treatment

Approximately 16 percent of the 453 patients who received REMERON™ in US 6-week controlled clinical trials discontinued treatment due to an adverse experience, compared to 7 percent of the 361 placebo-treated patients in those studies. The most common events ($\geq 1\%$) associated with discontinuation and considered to be drug related (i.e., those events associated with dropout at a rate at least twice that of placebo) included:

Common Adverse Events Associated with Discontinuation of Treatment in 6-Week US Remeron Trials		
Adverse Event	Percentage of Patients Discontinuing with Adverse Event	
	Remeron™ (n=453)	Placebo (n=361)
Somnolence	10.4%	2.2%
Nausea	1.5%	0%

Commonly Observed Adverse Events in US Controlled Clinical Trials

The most commonly observed adverse events associated with the use of REMERON™ (incidence of 5% or greater) and not observed at an equivalent incidence among placebo-treated patients (REMERON™ incidence at least twice that for placebo) were:

Common Treatment-Emergent Adverse Events Associated with the Use of Remeron in 6-Week US Trials		
Adverse Event	Percentage of Patients Reporting Adverse Event	
	Remeron TM (n=453)	Placebo (n=361)
Somnolence	54%	18%
Increased Appetite	17%	2%
Weight Gain	12%	2%
Dizziness	7%	3%

Adverse Events Occurring at an Incidence of 1% or More Among REMERONTM Treated Patients

The table that follows enumerates adverse events that occurred at an incidence of 1% or more, and were more frequent than in the placebo group, among REMERONTM-treated patients who participated in short-term U.S. placebo-controlled trials in which patients were dosed in a range of 5 to 60 mg/day. This table shows the percentage of patients in each group who at least one episode of an event at some time during their treatment. Reported adverse events were classified using a standard COSTART-based dictionary terminology.

The prescriber should be aware that these figures cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those which prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other investigations involving different treatments, uses and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and non-drug factors to the side effect incidence rate in the population studied.



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TABLE 2
INCIDENCE OF ADVERSE CLINICAL EXPERIENCES¹
(> 1%)
IN SHORT-TERM U.S. CONTROLLED STUDIES

Body System Adverse Clinical Experience	Remeron™ (N=453)	Placebo (N=361)
Body as a Whole		
Asthenia	8%	5%
Flu Syndrome	5%	3%
Back Pain	2%	1%
Digestive System		
Dry Mouth	25%	15%
Increased Appetite	17%	2%
Constipation	13%	7%
Metabolic and Nutritional Disorders		
Weight Gain	12%	2%
Peripheral Edema	2%	1%
Edema	1%	0%
Musculoskeletal System		
Myalgia	2%	1%
Nervous System		
Somnolence	54%	18%
Dizziness	7%	3%
Abnormal Dreams	4%	1%
Thinking Abnormal	3%	1%
Tremor	2%	1%
Confusion	2%	0%
Respiratory System		
Dyspnea	1%	0%
Urogenital System		
Urinary Frequency	2%	1%

¹ Events reported by at least 1% of patients treated with Remeron™(mirtazapine) are included, except the following events which had an incidence on placebo ≥ Remeron™: headache, infection, pain, chest pain, palpitation, tachycardia, postural hypotension, nausea, dyspepsia, diarrhea, flatulence, insomnia, nervousness, libido decreased, hypertonia, pharyngitis, rhinitis, sweating, amblyopia, tinnitus, taste perversion.



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ECG Changes

In an analysis of ECGs obtained in U.S. placebo-controlled clinical trials, REMERON™ and placebo-treated patients had a similar incidence of abnormal changes from baseline at 6-8 weeks of approximately 3%. The abnormalities were generally not considered clinically significant.

Other Adverse Events Observed During the Premarketing Evaluation of REMERON™

During its premarketing assessment, multiple doses of REMERON™ (mirtazapine) were administered to 2796 patients in clinical studies. The conditions and duration of exposure to mirtazapine varied greatly, and included (in overlapping categories) open and double-blind studies, uncontrolled and controlled studies, inpatient and outpatient studies, fixed dose and titration studies. Untoward events associated with this exposure were recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of untoward events into a smaller number of standardized event categories.

In the tabulations that follow, reported adverse events were classified using a standard COSTART-based dictionary terminology. The frequencies presented, therefore, represent the proportion of the 2796 patients exposed to multiple doses of REMERON™ who experienced an event of the type cited on at least one occasion while receiving REMERON™. All reported events are included except those already listed in the previous table, those adverse experiences subsumed under COSTART terms that are either overly general or excessively specific so as to be uninformative, and those events for which a drug cause was very remote.

It is important to emphasize that, although the events reported occurred during treatment with REMERON™, they were not necessarily caused by it.

Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse events are those occurring on one or more occasions in at least 1/100 patients; infrequent adverse events are those occurring in 1/100 to 1/1000 patients; rare events are those occurring in fewer than 1/1000 patients. Only those events not already listed in table 2 the previous table appear in this listing. Events of major clinical importance are also described in the WARNINGS and PRECAUTIONS sections.

Body as a whole: *frequent:* malaise, abd. minal pain, abdominal syndrome acute; *infrequent:* chills, fever, face edema, ulcer, photosensitivity reaction, neck rigidity, neck pain, abdomen enlarged; *rare:* cellulitis, chest pain substernal.

Cardiovascular System: *frequent:* hypertension, vasodilation; *infrequent:* angina pectoris, myocardial infarction, bradycardia, ventricular extrasystoles, syncope, migraine, hypotension; *rare:* atrial arrhythmia, bigeminy, vascular headache, pulmonary embolus, cerebral ischemia, cardiomegaly, phlebitis, left heart failure.



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Digestive System: *frequent*: vomiting, anorexia; *infrequent*: eructation, glossitis, cholecystitis, nausea and vomiting, gum hemorrhage, stomatitis, colitis, liver function tests abnormal; *rare*: tongue discoloration, ulcerative stomatitis, salivary gland enlargement, increased salivation, intestinal obstruction, pancreatitis, aphthous stomatitis, cirrhosis of liver, gastritis, gastroenteritis, oral moniliasis, tongue edema.

Endocrine System: *rare*: goiter, hypothyroidism.

Hemic and Lymphatic System: *rare*: lymphadenopathy, leukopenia, petechia, anemia, thrombocytopenia, lymphocytosis, pancytopenia.

Metabolic and Nutritional Disorders: *frequent*: thirst; *infrequent*: dehydration, weight loss, *rare*: gout, SGOT increased, healing abnormal, acid phosphatase increased, SGPT increased, diabetes mellitus.

Musculoskeletal System: *frequent*: myasthenia, arthralgia; *infrequent*: arthritis, tenosynovitis; *rare*: pathological fracture, osteoporosis fracture, bone pain, myositis, tendon rupture, arthrosis, bursitis.

Nervous System: *frequent*: hypesthesia, apathy, depression, hypokinesia, vertigo, twitching, agitation, anxiety, amnesia, hyperkinesia, paresthesia; *infrequent*: ataxia, delirium, delusions, depersonalization, dyskinesia, extrapyramidal syndrome, libido increased, coordination abnormal, dysarthria, hallucinations, manic reaction, neurosis, dystonia, hostility, reflexes increased, emotional lability, euphoria, paranoid reaction; *rare*: aphasia, nystagmus, akathisia, stupor, dementia, diplopia, drug dependence, paralysis, grand mal convulsion, hypotonia, myoclonus, psychotic depression, withdrawal syndrome.

Respiratory Systems: *frequent*: cough increased, sinusitis; *infrequent*: epistaxis, bronchitis, asthma, pneumonia; *rare*: asphyxia, laryngitis, pneumothorax, hiccup.

Skin and Appendages: *frequent*: pruritus, rash; *infrequent*: acne, exfoliative dermatitis, dry skin, herpes simplex, alopecia; *rare*: urticaria, herpes zoster, skin hypertrophy, seborrhea, skin ulcer.

Special Senses: *infrequent*: eye pain, abnormality of accommodation, conjunctivitis, deafness, keratoconjunctivitis, lacrimation disorder, glaucoma, hyperacusis, ear pain; *rare*: blepharitis, partial transitory deafness, otitis media, taste loss, parosmia.

Urogenital System: *frequent*: urinary tract infection; *infrequent*: kidney calculus, cystitis, dysuria, urinary incontinence, urinary retention, vaginitis, hematuria, breast pain, amenorrhea, dysmenorrhea, leukorrhea, impotence, *rare*: polyuria, urethritis, metrorrhagia, menorrhagia, abnormal ejaculation, breast engorgement, breast enlargement, urinary urgency.

DRUG ABUSE AND DEPENDENCE

Controlled Substance Class

REMERON™ (mirtazapine) Tablets are not a controlled substance.

Physical and Psychologic Dependence

REMERON™ (mirtazapine) has not been systematically studied in animals or humans for its potential for abuse, tolerance or physical dependence. While the clinical trials did not reveal any tendency for any drug-seeking behavior, these observations were not systematic and it is not possible to predict on the basis of this limited experience the extent to which a CNS-active drug will be misused, diverted and/or abused once marketed. Consequently, patients should be evaluated carefully for history of drug abuse, and such patients should be observed closely for signs of mirtazapine misuse or abuse (e.g., development of tolerance, incrementations of dose, drug-seeking behavior).

OVERDOSAGE

Human Experience

There is very limited experience with REMERON™ (mirtazapine) overdose. In premarketing clinical studies, there were nine eight reports of mirtazapine overdose alone or in combination with other pharmacological agents. The only drug overdose death reported while taking REMERON™ (mirtazapine) Tablets was in combination with amitriptyline and chlorprohixene in a non-U.S. clinical study. Based on plasma levels, the REMERON™ dose taken was 30-45 mg, while plasma levels of amitriptyline and chlorprohixene were found to be at toxic levels. All other premarketing overdose cases resulted in full recovery. Signs and symptoms reported in association with overdose included disorientation, drowsiness, impaired memory, and tachycardia. There were no reports of ECG abnormalities, coma or convulsions following overdose with REMERON™ alone.

Overdose Management

Treatment should consist of those general measures employed in the management of overdose with any antidepressant. There are no specific antidotes for REMERON™. If the patient is unconscious, establish and maintain an airway to ensure adequate oxygenation and ventilation. Gastric evacuation either by the induction of emesis or lavage or both should be considered. Activated charcoal should also be considered in treatment of overdose. Cardiac and vital signs monitoring is recommended along with general symptomatic and supportive measures.

In managing overdosage, consider the possibility of multiple-drug involvement. The physician should consider contacting a poison control center for additional information on the treatment of any overdose.



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DOSAGE AND ADMINISTRATION

Initial Treatment

The recommended starting dose for REMERON™ (mirtazapine) is 15 mg/day, administered in a single dose, preferably in the evening prior to sleep. In the controlled clinical trials establishing the antidepressant efficacy of REMERON™, the effective dose range was generally 15-45 mg/day. While the relationship between dose and antidepressant response for REMERON™ has not been adequately explored, patients not responding to the initial 15 mg dose may benefit from dose increases up to a maximum of 45 mg/day. REMERON™ has an elimination half-life of approximately 20-40 hours, therefore, dose changes should not be made at intervals of less than one to two weeks in order to allow sufficient time for evaluation of the therapeutic response to a given dose.

Elderly and Patients with Renal or Hepatic Impairment

The clearance of mirtazapine is reduced in elderly patients and in patients with moderate to severe renal or hepatic impairment. Consequently, the prescriber should be aware that plasma mirtazapine levels may be increased in these patient groups, compared to levels observed in younger adults without renal or hepatic impairment. (See Pharmacokinetics Subsection of CLINICAL PHARMACOLOGY).

Maintenance/Extended Treatment

There is no body of evidence available from controlled trials to indicate how long the depressed patient should be treated with REMERON™. It is generally agreed, however, that pharmacological treatment for acute episodes of depression should continue for up to six months or longer. Whether the dose of antidepressant needed to induce remission is identical to the dose needed to maintain euthymia is unknown.

Switching Patients to or from a Monoamine Oxidase Inhibitor

At least 14 days should elapse between discontinuation of an MAOI and initiation of therapy with REMERON™. In addition, at least 14 days should be allowed after stopping REMERON™ before starting an MAOI.

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HOW SUPPLIED

REMERON™ (mirtazapine) Tablets are supplied as:

15 mg Tablets - oval, scored, yellow, coated, with "Organon" embossed on one side and "TZ3" on the other side.

Bottles of 30	NDC # 0052-0105-30
Bottles of 100	NDC # 0052-0105-91
Bottles of 500	NDC # 0052-0105-95
Unit Dose, Box of 100	NDC # 0052-0105-90*

30 mg Tablets - oval, scored, red-brown, coated, with "Organon" embossed on one side and "TZ5" on the other side.

Bottles of 30	NDC # 0052-0107-30
Bottles of 100	NDC # 0052-0107-91
Bottles of 500	NDC # 0052-0107-95
Unit Dose, Box of 100	NDC # 0052-0107-90*

*Unit dose packs are provided as a blisterpack with 10 strips, each of which contain 10 tablets.

Store at controlled Room Temperature
20°-25°C (68°-77°F)

Dispense in a tight, light resistant container.

Caution: Federal law prohibits dispensing without prescription.



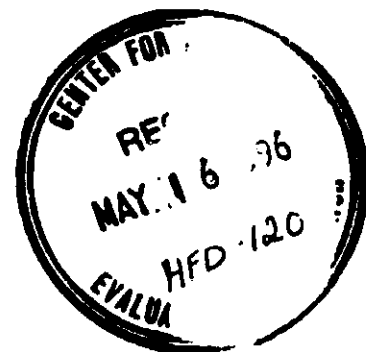
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Organon Inc.

May 15, 1996

Paul Leber, M.D., Director
Division of Neuropharmacological Drug Products
Center for Drug Evaluation and Research (HFD-120)
Woodmont II Building, 4th Floor
1451 Rockville Pike
Rockville, MD 20857

REF: NDA 20-415
REMERON™ (mirtazapine) Tablets



Dear Dr. Leber:

Reference is made to NDA No. 20-415 for Remeron™ (mirtazapine) Tablets, and to our correspondence of May 10, 1996 in which we provided final printed immediate container and carton labels for Remeron™ Tablets in Attachment V of that submission.

Three carton labels were inadvertently omitted from Attachment V. We have attached them to this letter and have assigned page numbers with the suffix "A" to correspond with the respective bottle labels found in the aforementioned May 10 submission. For example, the bottle label found on page 0003 of the May 10 submission has the corresponding carton label on page 0003A of this May 15 submission. The carton labels attached are as follow:

- Carton Label for Bottles of 100 Remeron™ 15mg Tablets (page 0003A)
- Carton Label for Bottles of 500 Remeron™ 30mg Tablets (page 00012A)
- Hospital Unit Dose Carton Label for Remeron™ 30mg Tablets (page 00013A)

We are providing 12 copies of each of the items specified above.



Organon Inc.
375 Mt. Pleasant Avenue
West Orange
New Jersey 07052
USA
Tel.: (201) 325-4500
Fax: (201)-325-4589

CONFIDENTIAL

Paul Leber, M.D.

May 15, 1996

Remeron™ (mirtazapine) Tablets, NDA 20-415

Page 2

Please note that Organon Inc. regards this application and all correspondence related thereto as confidential, trade secret and proprietary information and hereby claims protection from disclosure under the applicable sections of 18 U.S.C. and 21 CFR.

Should you have any questions regarding this submission, please contact the undersigned at (201) 325-4837.

Sincerely,

Loan T. Tran

Loan T. Tran, Pharm. D.

Assistant Director, Regulatory Affairs

Submitted to NDA 20-415 via Federal Express No. 9134949434

cc: Mr. Paul David (2 desk copies)



CONFIDENTIAL

Organon Inc.

May 10, 1996

Paul Leber, M.D., Director
Division of Neuropharmacological Drug Products
Center for Drug Evaluation and Research (HFD-120)
Woodmont II Building, 4th Floor
1451 Rockville Pike
Rockville, MD 20857

Re: NDA 20-415
REMERON™ (mirtazapine) Tablets

Dear Dr. Leber:

Reference is made to Organon Inc. NDA No. 20-415 for Remeron™ (mirtazapine) Tablets, to our resubmission of January 26, 1995 and to the approvable letter dated January 26, 1996. Reference is further made to the April 23, 1996 meeting between the Agency and Organon during which the labeling, phase 4 commitments and chemistry were discussed; to your letter dated April 19, 1996 requesting a world literature update; to your letter dated April 22, 1996 requesting copies of approved foreign labeling and comment on any negative regulatory action; to the April 25, 1996 teleconference between Mr. P. David of FDA and Dr. L. Tran of Organon during which we were informed of your decision to approve initially a 24-month expiration dating period for Remeron™ tablets but that such dating could be extended by Organon by submitting real time stability data as General Correspondence to the NDA; to the May 1, 1996 teleconference between Mr. P. David of FDA and Dr. L. Tran of Organon during which we were informed of your decision to remove your proposal for a boxed warning for agranulocytosis and were requested to provide a written commitment to conduct a fixed-dose response/somnolence and a relapse prevention as Phase IV studies; and to the May 6, 1996 faxed copy of the second FDA draft labeling for Remeron™. Organon hereby responds to all of the above outstanding items:

◆ World Literature Update:

A comprehensive world archival literature search was conducted covering the period from the NDA filing to the present (1994 to 1996). A systematic and detailed review of the identified references found nothing that would adversely affect conclusions about the safety of Remeron™. This world literature update report is provided in Attachment N.

Organon

Organon Inc.
375 Mt. Pleasant Avenue
West Orange
New Jersey 07052
USA
Tel: (201) 325-4500
Fax: (201) 325-4589

May 10, 1996

Remeron™ (mirtazapine) Tablets, NDA 20-415

Page 2

◆ **Regulatory Update: Foreign Labeling and Any Negative Action**

As previously communicated, Remeron™ is currently approved in the Netherlands, Finland, Denmark, Germany, Argentina, Austria, Greece, Spain, Sweden, Brazil, Ecuador and Peru. On November 6, 1995 we submitted to the NDA the English translation of the labeling for the Netherlands, Finland, Austria and Peru. Attachment 2 contains a copy of all currently approved foreign labeling (with an English translation).

There has been no negative regulatory action taken on Remeron™.

◆ **Chemistry: Statistical Analysis of Stability Data**

Organon acknowledges the Agency decision to approve an initial 24-month expiration dating period based on the currently available 24-month data, but that the expiry period may be extended in the future (when real time data becomes available on these lots) only by notification to FDA in General Correspondence to the NDA.

◆ **Clinical: Phase 4 Commitments**

Based on the information provided to us during the May 1, 1996 telephone discussion mentioned above, Organon hereby commits to conduct a fixed dose response/somnolence study and a relapse prevention study. We note that the Agency had agreed to remove the request for the pediatric studies during our April 23, 1996 meeting.

We will provide you draft protocols for each of these studies as soon as practicable. We expect to start those studies in early 1997 and estimate study completion by mid 1998 and early 1999, respectively.

May 10, 1996

Remeron™ (mirtazapine) Tablets, NDA 20-415

Page 3

◆ Labeling

We acknowledge receipt by fax of the second draft of the proposed labeling for Remeron™. Organon accepts the labeling as proposed, with the exception of two minor corrections that have been conveyed to Mr. P. David by telephone on May 9, 1996. Specifically, in the Overdose section, the number of overdose cases in premarketing clinical studies was corrected to 8 rather than 9 cases; and in the Warnings for agranulocytosis, the time of onset have been reordered to match the cases discussed in the previous sentence, i.e. day 61 for the agranulocytosis case, day 9 for the Sjögren's case, and day 14 for the asymptomatic severe neutropenia case. Additionally, we also removed reference to the 1% incidence table as "Table 2" since other tables in the package insert are not numbered. The final draft version of the labeling, reflecting the above changes (in red-line/strike-out format), is provided in Attachment 4. Final printed labeling will be submitted as soon as it is practicable.

Additionally, in Attachment 5, we are providing the final printed immediate container and carton labels for Remeron™ Tablets, including those for professional samples.

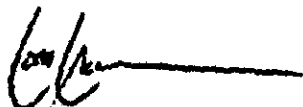
The draft introductory promotional materials and copies of the cited references will be submitted to both the Division and the Division of Drug Marketing and Communication early next week. We would appreciate your review and comment as quickly as possible.

We trust that all outstanding items have been adequately addressed, and look forward to final approval of the NDA for Remeron™ Tablets.

Please note that Organon Inc. regards this application and all correspondence related thereto as confidential, trade secret and proprietary information and hereby claims protection from disclosure under the applicable sections of 18 U.S.C. and 21 CFR.

Should you have any questions regarding this submission, please contact the undersigned at (201) 325-4837.

Sincerely,



Loan T. Tran, Pharm. D.
Assistant Director
Regulatory Affairs

cc: Mr. Paul David, Project Manager (2 desk copies)
Dr. Robert Temple, Director, Office of Drug Evaluation I (letter only)

Submitted to NDA 20-415 via Federal Express No. 8092928071

MEETING MINUTES

Date: April 23, 1996; 2:15 - 4:00 PM
NDA #: 20-415
Location: Conference Room E; WOC2
Firm: Organon
Drug: Remeron (mirtazapine)
Indication: Depression
Meeting Type: Discuss Labeling/Phase 4 Commitments
Participants:

FDA Attendees and Titles:

Robert Temple, M.D.	Office Director
Paul Leber, M.D.	Division Director
Thomas Laughren, M.D.	Group Leader
Glenna Fitzgerald, Ph.D.	Supervisory Pharmacologist
Barry Rosloff, Ph.D.	Reviewing Pharmacologist
Andrew Mosholder, M.D.	Clinical Reviewer
John Balian, M.D.	Clinical Reviewer
Greg Burkhart, M.D.	Safety Group Reviewer
Safaa Ibrahim, Ph.D.	Biopharmaceutic Reviewer
Paul David, R.Ph.	Project Manager

External Participant Attendees and Titles: See attached list

PURPOSE

The meeting was requested by the sponsor to discuss their resubmission dated March 15, 1996, providing for a response to an Agency approvable letter dated January 26, 1996. The sponsor wished to discuss labeling issues and Phase 4 commitments.

DISCUSSION

- **Boxed warning for agranulocytosis:** Organon does not believe that 3 cases of agranulocytosis warrants a boxed warning. Agency stated that no agranulocytosis noted in any of the clinical databases of last 5 approved antidepressants. No resolution. Agency will consider Organon's proposal to remove box, as well as Organon's request to remove confidence intervals in the agranulocytoses text.
- **Phase 4 commitments:** Organon intends to conduct an exploration of dose response and time course for sedative effects of mirtazapine, however they do not wish to conduct the other Phase 4 commitments, i.e., pediatric depression studies, exploration of dose response for effectiveness, and long-term efficacy studies. The Agency suggested combining the dose response efficacy study with the sedation study. Organon stated that they would consider this. Due to the cases of agranulocytosis, the Agency agreed that a pediatric depression study would not be necessary. The sponsor stated that they would conduct a long-term efficacy study if boxed warning removed.
- **Smokers subsection of the Pharmacokinetics section:** The sponsor requested the analysis on how the Agency came to its conclusion. The Agency replied that it pooled the pharmacokinetic data from healthy normals. This data to be given to the sponsor for review.

- **Pharmacodynamics subsection of CLINICAL PHARMACOLOGY section:** Could not reach agreement on some parts of this section. Decision was to have an outside committee consisting of the regulatory affairs staff and pharmacologists from both Organon and the Agency work on agreement.
- **Somnolence subsection of PRECAUTIONS section:** The sponsor wishes to remove the statement concerning the motor vehicle accidents (MVAs) associated with Remeron. Agency stated that they would remove this statement if sponsor agreed to bold the last sentence relating to a decrease in alertness due to sedative effects of drug. Organon stated that they would consider this proposal.

CONCLUSIONS/UNRESOLVED ISSUES

- Dr. Temple to consider the issue of a box for agranulocytosis.
- Sponsor to get back with Agency concerning agreement to conduct long-term study and dose response for efficacy study.
- Agency to provide sponsor with smoking data, i.e., pooling of patients analysis.
- Committee to meet to discuss and resolve Pharmacodynamics section.
- Sponsor to consider the removal of MVA statement in Somnolence subsection but have last line in subsection in bold print.
- Since time did not permit for discussion of all of the labeling, Agency to fax sponsor revised version which incorporates some of sponsor's revisions. This will facilitate focused discussion of the areas of labeling which need to be further discussed.



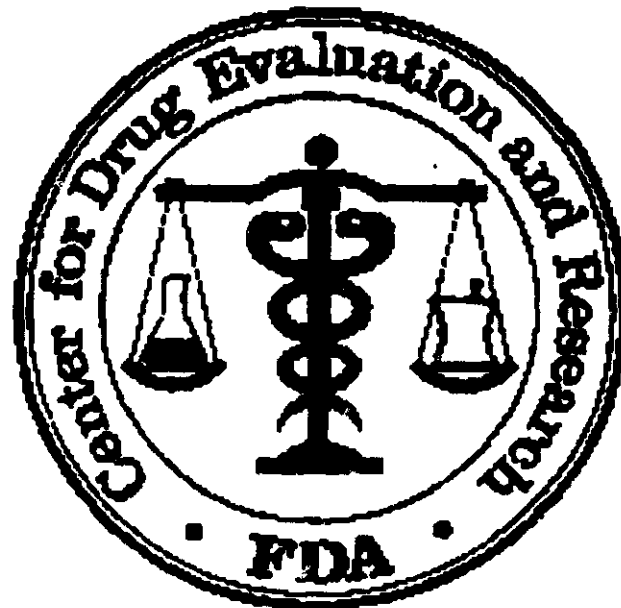
Paul A. David, R.Ph.
Regulatory Management Officer

Attachments (1)

- (1) Correspondence from sponsor with list of attendees and agenda items

FOOD AND DRUG ADMINISTRATION
DIVISION OF NEUROPHARMACOLOGICAL
DRUG PRODUCTS
DOCUMENT CONTROL ROOM, HFD-120
5600 FISHERS LANE
ROCKVILLE, MARYLAND 20857

DATE May 6, 1996



TO:

Name Loan Tran, Pharm.D.

Fax No. (201) 325-4769

Phone No. (201) 325-4837

Location Organon

FROM:

Name Paul David, R.Ph.

Fax No. (301) 594-2859

Phone No. (301) 594-2777

Location FDA:CDER:ODE1:HFD-120

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Comments:

Loan

I am faxing you a revised version of the Remeron labeling. Note: Labeling consists of pages 1-20.

Paul

ATTACHMENT

REMERON™ (mirtazapine) Tablets

DESCRIPTION

REMERON™ (mirtazapine) is an antidepressant for oral administration. It has a tetracyclic chemical structure unrelated to selective serotonin reuptake inhibitors, tricyclics or monoamine oxidase inhibitors (MAOI). Mirtazapine belongs to the piperazino-azepine group of compounds. It is designated 1,2,3,4,10,14b-hexahydro-2-methylpyrazino [2,1-a] pyrido [2,3-c] benzazepine and has the empirical formula of $C_{17}H_{19}N_3$. Its molecular weight is 265.36. The structural formula is the following and it is the racemic mixture:

[Insert structural formula here.]

Mirtazapine is a white to creamy white crystalline powder which is slightly soluble in water.

REMERON™ is supplied for oral administration as scored film-coated tablets containing 15 or 30 mg of mirtazapine. Each tablet also contains corn starch, hydroxypropyl cellulose, magnesium stearate, colloidal silicon dioxide, lactose and other inactive ingredients.

CLINICAL PHARMACOLOGY

Pharmacodynamics

The mechanism of action of REMERON™ (mirtazapine), as with other antidepressants, is unknown.

Evidence gathered in preclinical studies suggests that mirtazapine enhances central noradrenergic and serotonergic activity. These studies have shown that mirtazapine acts as an antagonist at central presynaptic α_2 adrenergic inhibitory

autoreceptors and heteroreceptors, an action that is postulated to result in an increase in central noradrenergic and serotonergic activity.

Mirtazapine is a potent antagonist of 5-HT₂ and 5-HT₁ receptors. Mirtazapine has no significant affinity for the 5-HT_{1A} and 5-HT_{1B} receptors.

Mirtazapine is a potent antagonist of histamine (H₁) receptors, a property that may explain its prominent sedative effects.

Mirtazapine is a moderate peripheral α_1 adrenergic antagonist, a property that may explain the occasional orthostatic hypotension reported in association with its use.

Mirtazapine is a moderate antagonist at muscarinic receptors, a property that may explain the relatively low incidence of anticholinergic side effects associated with its use.

Pharmacokinetics

REMERON™ (mirtazapine) is rapidly and completely absorbed following oral administration and has a half-life of about 20-40 hours. Peak plasma concentrations are reached within about 2 hours following an oral dose. The presence of food in the stomach has a minimal effect on both the rate and extent of absorption and does not require a dosage adjustment.

Mirtazapine is extensively metabolized after oral administration. Major pathways of biotransformation are demethylation and hydroxylation followed by glucuronide conjugation. In-vitro data from human liver microsomes indicate that cytochrome 2D6 and 1A2 are involved in the formation of the 8-hydroxy metabolite of mirtazapine, whereas cytochrome 3A is considered to be responsible for the formation of the N-desmethyl and N-oxide metabolite. Mirtazapine has an absolute bioavailability of about 50%. It is eliminated predominantly via urine (75%) with 15% in feces. Several unconjugated metabolites possess pharmacological activity but are present in the plasma at very low levels. The (-) enantiomer has an elimination half-life that is approximately twice as long as the (+) enantiomer and therefore achieves plasma levels that are about three times as high as that of the (+) enantiomer.

Plasma levels are linearly related to dose over a dose range of 15 to 80 mg. The mean elimination half-life of mirtazapine

after oral administration ranges from approximately 20-40 hours across age and gender subgroups, with females of all ages exhibiting significantly longer elimination half-lives than males (mean half-life of 37 hours for females vs 26 hours for males). Steady state plasma levels of mirtazapine are attained within 5 days, with about 50% accumulation (accumulation ratio = 1.5).

Mirtazapine is approximately 85% bound to plasma proteins over a concentration range of 0.01 to 10 µg/mL.

Population Subgroups

Liver Disease - Following a single 15 mg oral dose of mirtazapine, the oral clearance of mirtazapine was decreased by approximately 30% in hepatically impaired patients compared to subjects with normal hepatic function. Caution is indicated in administering REMERON™ to patients with compromised hepatic function (see Precautions and Dosage and Administration).

Renal Disease - Following a single 15 mg oral dose of mirtazapine, patients with moderate [glomerular filtration rate (GFR) = 11-39 mL/min/1.73 m²] and severe [GFR < 10 mL/min/1.73 m²] renal impairment had reductions in mean oral clearance of mirtazapine of about 30% and 50%, respectively, compared to normal subjects. Caution is indicated in administering REMERON™ to patients with compromised renal function (see Precautions and Dosage and Administration).

Elderly Patients - Following oral administration of mirtazapine 20 mg/day for 7 days to subjects of varying ages (range, 25-74), oral clearance of mirtazapine was reduced in the elderly compared to the younger subjects. The differences were most striking in males, with a 40% lower clearance in elderly males compared to younger males, while the clearance in elderly females was only 10% lower compared to younger females. Caution is indicated in administering REMERON™ to elderly patients (see Precautions and Dosage and Administration).

Clinical Trials Showing Effectiveness

The efficacy of REMERON™ (mirtazapine) as a treatment for depression was established in four placebo-controlled, 6-week trials in adult outpatients meeting DSM-III criteria for major depression. Patients were titrated with mirtazapine from a dose range of 5 mg up to 35 mg/day. Overall, these studies

demonstrated mirtazapine to be superior to placebo on at least three of the following four measures: 21-Item Hamilton Depression Rating Scale (HDRS) total score; HDRS Depressed Mood Item; CGI Severity score; and Montgomery and Asberg Depression Rating Scale (MADRS). Superiority of mirtazapine over placebo was also found for certain factors of the HDRS including anxiety/somatization factor and sleep disturbance factor. The mean mirtazapine dose for patients who completed these four studies ranged from 21 to 32 mg/day. A fifth study of similar design utilized a higher dose (up to 50 mg) per day and also showed effectiveness.

Examination of age and gender subsets of the population did not reveal any differential responsiveness on the basis of these subgroupings.

INDICATIONS AND USAGE

REMERON™ (mirtazapine) Tablets are indicated for the treatment of depression.

The efficacy of REMERON™ in the treatment of depression was established in six week controlled trials of outpatients whose diagnoses corresponded most closely to the Diagnostic and Statistical Manual of Mental Disorders - 3rd edition (DSM-III) category of major depressive disorder (see CLINICAL PHARMACOLOGY).

A major depressive episode (DSM-IV) implies a prominent and relatively persistent (nearly every day for at least 2 weeks) depressed or dysphoric mood that usually interferes with daily functioning, and includes at least five of the following nine symptoms: depressed mood, loss of interest in usual activities, significant change in weight and/or appetite, insomnia or hypersomnia, psychomotor agitation or retardation, increased fatigue, feelings of guilt or worthlessness, slowed thinking or impaired concentration, a suicide attempt or suicidal ideation.

The antidepressant effectiveness of REMERON™ (mirtazapine) in hospitalized depressed patients has not been adequately studied.

The effectiveness of REMERON™ in long-term use, that is, for more than 6 weeks, has not been systematically evaluated in controlled trials. Therefore, the physician who elects to use REMERON™ for extended periods should periodically evaluate the

long-term usefulness of the drug for the individual patient.

CONTRAINDICATIONS

REMERON™ (mirtazapine) Tablets are contraindicated in patients with a known hypersensitivity to mirtazapine.

WARNINGS

Agranulocytosis

In premarketing clinical trials, two (one with Sjögren's Syndrome) out of 2,796 patients treated with REMERON™ (mirtazapine) Tablets developed agranulocytosis [absolute neutrophil count (ANC) $< 500/\text{mm}^3$ with associated signs and symptoms, e.g., fever, infection, etc.] and a third patient developed severe neutropenia [ANC $< 500/\text{mm}^3$ without any associated symptoms]. For these three patients, onset of severe neutropenia was detected on days 9, 14, and 61 of treatment, respectively. All three patients recovered after Remeron was stopped. These three cases yield a crude incidence of severe neutropenia (with or without associated infection) of approximately 1.1 per thousand patients exposed, with a very wide 95% confidence interval, i.e., 2.2 cases per 10,000 to 3.1 cases per 1000. If a patient develops a sore throat, fever, stomatitis or other signs of infection, along with a low WBC count, treatment with REMERON™ should be discontinued and the patient should be closely monitored.

MAO Inhibitors

In patients receiving other antidepressants in combination with a monoamine oxidase inhibitor (MAOI) and in patients who have recently discontinued an antidepressant drug and then are started on an MAOI, there have been reports of serious, and sometimes fatal, reactions, e.g., including nausea, vomiting, flushing, dizziness, tremor, myoclonus, rigidity, diaphoresis, hyperthermia, autonomic instability with rapid fluctuations of vital signs, seizures, and mental status changes ranging from agitation to coma. Although there are no human data pertinent to such an interaction with REMERON™, it is recommended that REMERON™ not be used in combination with an MAOI, or within 14 days of initiating or discontinuing therapy with an MAOI.

PRECAUTIONS

General

Somnolence

In U.S. controlled studies, somnolence was reported in 54% of patients treated with REMERON™ (mirtazapine), compared to 18% for placebo and 60% for amitriptyline. In these studies, somnolence resulted in discontinuation for 10.4% of Remeron treated patients, compared to 2.2% for placebo. It is unclear whether or not tolerance develops to the somnolent effects of Remeron. Because of Remeron's potentially significant effects on impairment of performance, patients should be cautioned about engaging in activities requiring alertness until they have been able to assess the drug's effect on their own psychomotor performance (see Information for Patients).

Dizziness

In U.S. controlled studies, dizziness was reported in 7% of patients treated with REMERON™ (mirtazapine), compared to 3% for placebo and 14% for amitriptyline. It is unclear whether or not tolerance develops to the dizziness observed in association with the use of Remeron.

Increased Appetite/Weight Gain

In US controlled studies, appetite increase was reported in 17% of patients treated with REMERON™ (mirtazapine), compared to 2% for placebo and 6% for amitriptyline. In these same trials, weight gain of $\geq 7\%$ of body weight was reported in 7.5% of patients treated with mirtazapine, compared to 0% for placebo and 5.9% for amitriptyline. In a pool of premarketing US studies, including many patients in long-term, open label treatment, 8% of patients receiving Remeron discontinued for weight gain.

Cholesterol/Triglycerides

In U.S. controlled studies, nonfasting cholesterol increases to $\geq 20\%$ above the upper limits of normal were observed in 15% of patients treated with REMERON™ (mirtazapine), compared to 7% for placebo and 8% for amitriptyline. In these same studies, nonfasting triglyceride increases to ≥ 500 mg/dL were observed in 6% of patients treated with mirtazapine, compared to 3% for placebo and 3% for amitriptyline.

Transaminase Elevations

Clinically significant ALT (SGPT) elevations (≥ 3 times the upper limit of the normal range) were observed in 2.0% (8/424) of patients exposed to Remeron in a pool of short-term US controlled trials, compared to 0.3% (1/328) of placebo patients and 2.0% (3/181) of amitriptyline patients. Most of these patients with ALT increases did not develop signs or symptoms associated with compromised liver function. While some patients were discontinued for the ALT increases, in other cases, the enzyme levels returned to normal despite continued REMERON[™] (mirtazapine) treatment. Mirtazapine should be used with caution in patients with impaired hepatic function (see Pharmacokinetics section of Clinical Pharmacology, and Dosage and Administration).

Activation of Mania/Hypomania

Mania/hypomania occurred in approximately 0.2% (3/1,299 patients) of REMERON[™] (mirtazapine) treated patients in U.S. studies. Although the incidence of mania/hypomania was very low during treatment with mirtazapine, it should be used carefully in patients with a history of mania/hypomania.

Seizures

In pre-marketing clinical trials only one seizure was reported among the 2,796 U.S. and non-U.S. patients treated with REMERON[™] (mirtazapine). However, no controlled studies have been carried out in patients with a history of seizures. Therefore, care should be exercised when mirtazapine is used in these patients.

Suicide

Suicidal ideation is inherent in depression and may persist until significant remission occurs. As with any patient receiving antidepressants, high-risk patients should be closely supervised during initial drug therapy. Prescriptions of REMERON[™] (mirtazapine) should be written for the smallest quantity consistent with good patient management, in order to reduce the risk of overdose.

Use in patients with concomitant illness

Clinical experience with REMERON[™] (mirtazapine) 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.

Mirtazapine 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. Mirtazapine was not associated with clinically significant ECG abnormalities in U.S. and non-U.S. placebo controlled trials. Mirtazapine 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™ 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).

Mirtazapine clearance is decreased in patients with moderate [glomerular filtration rate (GFR) = 11-39 mL/min/1.73 m²] and severe [GFR < 10 mL/min/1.73 m²] renal impairment, and also in patients with hepatic impairment (See Pharmacokinetic Subsection of CLINICAL PHARMACOLOGY). Caution is indicated in administering REMERON™ to such patients (see DOSAGE AND ADMINISTRATION).

Information for patients

Physicians are advised to discuss the following issues with patients for whom they prescribe REMERON™:

Agranulocytosis

Patients who are to receive REMERON™ (mirtazapine) should be warned about the risk of developing agranulocytosis. Patients should be advised to contact their physician if they experience any indication of infection such as fever, chills, sore throat, mucous membrane ulceration or other possible signs of infection. Particular attention should be paid to any flu-like complaints or other symptoms that might suggest infection.

Interference with Cognitive and Motor Performance

REMERON™ (mirtazapine) may impair judgement, thinking, and, particularly, motor skills, because of its prominent sedative effect. The drowsiness associated with mirtazapine use may impair a patient's ability to drive, use machines or perform tasks that require alertness. Thus, patients should be cautioned about engaging in hazardous activities until they

are reasonably certain that Remeron therapy does not adversely affect their ability to engage in such activities.

Completing Course of Therapy

While patients may notice improvement with REMERON[™] (mirtazapine) therapy in 1 to 4 weeks, they should be advised to continue therapy as directed.

Concomitant medication

Patients should be advised to inform their physician if they are taking, or intend to take, any prescription or over-the-counter drugs since there is a potential for REMERON[™] (mirtazapine) to interact with other drugs.

Alcohol

The impairment of cognitive and motor skills produced by REMERON[™] (mirtazapine) has been shown to be additive with those produced by alcohol. Accordingly, patients should be advised to avoid alcohol while taking mirtazapine.

Pregnancy

Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during REMERON[™] (mirtazapine) therapy.

Nursing

Patients should be advised to notify their physician if they are breast-feeding an infant.

Laboratory tests

There are no routine laboratory tests recommended.

Drug Interactions

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).

Drugs Affecting Hepatic Metabolism

The metabolism and pharmacokinetics of REMERON[™] (mirtazapine)

may be affected by the induction or inhibition of drug-metabolizing enzymes.

Drugs that are Metabolized by and/or Inhibit Cytochrome P450 Enzymes

Many drugs are metabolized by and/or inhibit various cytochrome P450 enzymes, e.g., 2D6, 1A2, 3A4, etc. In vitro studies have shown that REMERON™ (mirtazapine) is a substrate for several of these enzymes, including 2D6, 1A2, and 3A4. While in vitro studies have shown that mirtazapine is not a potent inhibitor of any of these enzymes, an indication that mirtazapine is not likely to have a clinically significant inhibitory effect on the metabolism of other drugs that are substrates for these cytochrome P450 enzymes, the concomitant use of mirtazapine with most other drugs metabolized by these enzymes has not been formally studied. Consequently, it is not possible to make any definitive statements about the risks of coadministration of mirtazapine with such drugs.

Alcohol

Concomitant administration of alcohol (equivalent to 60 g) had a minimal effect on plasma levels of REMERON™ (15 mg) in 6 healthy male subjects. However, the impairment of cognitive and motor skills produced by REMERON™ were shown to be additive with those produced by alcohol. Accordingly, patients should be advised to avoid alcohol while taking REMERON™.

Diazepam

Concomitant administration of diazepam (15 mg) had a minimal effect on plasma levels of mirtazapine (15 mg) in 12 healthy subjects. However, the impairment of motor skills produced by REMERON™ has been shown to be additive with those caused by diazepam. Accordingly, patients should be advised to avoid diazepam and other similar drugs while taking REMERON™.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Carcinogenicity studies were conducted with REMERON™ (mirtazapine) given in the diet at doses of 2, 20, and 200 mg/kg/day to mice and 2, 20, and 60 mg/kg/day to rats. The highest doses used are approximately 20 and 12 times the maximum recommended human dose (MRHD) of 45 mg/day on a mg/m²

basis in mice and rats, respectively. There was an increased incidence of hepatocellular adenoma and carcinoma in male mice at the high dose. In rats, there was an increase in hepatocellular adenoma in females at the mid and high doses and in hepatocellular tumors and thyroid follicular adenoma/cystadenoma and carcinoma in males at the high dose. The data suggest that the above effects could possibly be mediated by non-genotoxic mechanisms, the relevance of which to humans is not known.

The doses used in the mouse study may not have been high enough to fully characterize the carcinogenic potential of REMERON™.

Mutagenesis

REMERON™ was not mutagenic or clastogenic and did not induce general DNA damage as determined in several genotoxicity tests: Ames test, in vitro gene mutation assay in Chinese hamster V 79 cells, in vitro sister chromatid exchange assay in cultured rabbit lymphocytes, in vivo bone marrow micronucleus test in rats, and unscheduled DNA synthesis assay in HeLa cells.

Impairment of Fertility

In a fertility study in rats, Remeron™ was given at doses up to 20 times the maximum recommended human dose (MRHD) on a mg/m² basis. Mating and conception were not affected by the drug, but estrous cycling was disrupted at doses that were 3 or more times the MRHD and pre-implantation losses occurred at 20 times the MRHD.

Pregnancy

Teratogenic Effects - Pregnancy Category C

Reproduction studies in pregnant rats and rabbits at doses up to 20 and 17 times the maximum recommended human dose (MRHD) on a mg/m² basis, respectively, have revealed no evidence of teratogenic effects. However, in rats, there was an increase in post-implantation losses in dams treated with Remeron™ (mirtazapine). There was an increase in pup deaths during the first 3 days of lactation and a decrease in pup birth weights. The cause of these deaths is not known. These effects occurred at doses that were 20 times the MRHD, but not at 3 times the MRHD, on a mg/m² basis. There are no adequate and well controlled studies in pregnant women. Because animal

reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers

It is not known whether mirtazapine is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when REMERON™ (mirtazapine) Tablets are administered to nursing women.

Pediatric Use

Safety and effectiveness in children have not been established.

Geriatric Use

Approximately 190 elderly individuals (≥ 65 years of age) participated in clinical studies with Remeron. No unusual adverse age-related phenomena were identified in this group. Pharmacokinetic studies revealed a decreased clearance in the elderly. Caution is indicated in administering Remeron to elderly patients (see Clinical Pharmacology and Dosage and Administration).

ADVERSE REACTIONS

Associated with discontinuation of treatment

[Note to Firm: Please fill in the missing information in the following paragraph.]

Approximately 16 percent of the 453 patients who received Remeron in US 6-week controlled clinical trials discontinued treatment due to an adverse experience, [REDACTED]. The most common events ($\geq 1\%$) associated with discontinuation and considered to be drug related (i.e., those events associated with dropout at a rate at least twice that of placebo) included:

Common Adverse Events Associated with Discontinuation of Treatment in 6-Week US Remeron Trials		
Adverse Event	Percentage of Patients Discontinuing with Adverse Event	
	Remeron (n=453)	Placebo (n=361)
Somnolence	10.4%	2.2%
Nausea	1.5%	0%

Commonly Observed Adverse Events in US Controlled Clinical Trials

The most commonly observed adverse events associated with the use of REMERON™ (incidence of 5% or greater) and not observed at an equivalent incidence among placebo-treated patients (Remeron incidence at least twice that for placebo) were:

Common Treatment-Emergent Adverse Events Associated with the Use of Remeron in 6-Week US Trials		
Adverse Event	Percentage of Patients Reporting Adverse Event	
	Remeron (n=453)	Placebo (n=361)
Somnolence	54%	18%
Increased Appetite	17%	2%
Weight Gain	12%	2%
Dizziness	7%	3%

Adverse Events Occurring at an Incidence of 1% or More Among REMERON™ Treated Patients

The table that follows enumerates adverse events that occurred at an incidence of 1% or more, and were more frequent than in the placebo group, among Remeron-treated patients who participated in short-term U.S. placebo-controlled trials in which patients were dosed in a range of 5 to 60 mg/day. This table shows the percentage of patients in each group who had at least one episode of an event at some time during their treatment. Reported adverse events were classified using a standard COSTART-based dictionary terminology.

The prescriber should be aware that these figures cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those which prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other investigations involving different treatments, uses and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and non-drug factors to the side effect incidence rate in the population studied.

TABLE 2
INCIDENCE OF ADVERSE CLINICAL EXPERIENCES¹ (≥1%)
IN SHORT-TERM U.S. CONTROLLED STUDIES

Body System Adverse Clinical Experience	Org 3770 (N=453)	Placebo (N=361)
Body as a Whole		
Asthenia	8%	5%
Flu Syndrome	5%	3%
Back Pain	2%	1%
Digestive System		
Dry Mouth	25%	15%
Increased Appetite	17%	2%
Constipation	13%	7%
Metabolic and Nutritional Disorders		
Weight Gain	12%	2%
Peripheral Edema	2%	1%
Edema	1%	0%
Musculoskeletal System		
Myalgia	2%	1%
Nervous System		
Somnolence	54%	18%
Dizziness	7%	3%
Abnormal Dreams	4%	1%
Thinking Abnormal	3%	1%
Tremor	2%	1%
Confusion	2%	0%
Respiratory System		
Dyspnea	1%	0%
Urogenital System		
Urinary Frequency	2%	1%

¹ Events reported by at least 1% of patients treated with Remeron (mirtazapine) are included, except the following events which had an incidence on placebo ≥ Remeron:

headache, infection, pain, chest pain, palpitation, tachycardia, postural hypotension, nausea, dyspepsia, diarrhea, flatulence, insomnia, nervousness, libido decreased, hypertonia, pharyngitis, rhinitis, sweating, amblyopia, tinnitus, taste perversion.

ECG Changes

In an analysis of ECGs obtained in U.S. placebo-controlled clinical trials, REMERON™ and placebo-treated patients had a similar incidence of abnormal changes from baseline at 6-8 weeks of approximately 3%. The abnormalities were generally not considered clinically significant.

Other Adverse Events Observed During the Premarketing Evaluation of REMERON™

During its premarketing assessment, multiple doses of REMERON™ (mirtazapine) were administered to 2796 patients in clinical studies. The conditions and duration of exposure to mirtazapine varied greatly, and included (in overlapping categories) open and double-blind studies, uncontrolled and controlled studies, inpatient and outpatient studies, fixed dose and titration studies. Untoward events associated with this exposure were recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of untoward events into a smaller number of standardized event categories.

In the tabulations that follow, reported adverse events were classified using a standard COSTART-based dictionary terminology. The frequencies presented, therefore, represent the proportion of the 2796 patients exposed to multiple doses of Remeron who experienced an event of the type cited on at least one occasion while receiving Remeron. All reported events are included except those already listed in the previous table, those adverse experiences subsumed under COSTART terms that are either overly general or excessively specific so as to be uninformative, and those events for which a drug cause was very remote.

It is important to emphasize that, although the events reported occurred during treatment with Remeron, they were not necessarily caused by it.

Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse events are those occurring on one or more occasions in at least 1/100 patients; infrequent

adverse events are those occurring in 1/100 to 1/1000 patients; rare events are those occurring in fewer than 1/1000 patients. Only those events not already listed in Table 2 appear in this listing. Events of major clinical importance are also described in the WARNINGS and PRECAUTIONS sections.

Body as a whole: frequent: malaise, abdominal pain, abdominal syndrome acute; infrequent: chills, fever, face edema, ulcer, photosensitivity reaction, neck rigidity, neck pain, abdomen enlarged; rare: cellulitis, chest pain substernal.

Cardiovascular System: frequent: hypertension, vasodilatation; infrequent: angina pectoris, myocardial infarction, bradycardia, ventricular extrasystoles, syncope, migraine, hypotension; rare: atrial arrhythmia, bigeminy, vascular headache, pulmonary embolus, cerebral ischemia, cardiomegaly, phlebitis, left heart failure.

Digestive System: frequent: vomiting, anorexia; infrequent: eructation, glossitis, cholecystitis, nausea and vomiting, gum hemorrhage, stomatitis, colitis, liver function tests abnormal; rare: tongue discoloration, ulcerative stomatitis, salivary gland enlargement, increased salivation, intestinal obstruction, pancreatitis, aphthous stomatitis, cirrhosis of liver, gastritis, gastroenteritis, oral moniliasis, tongue edema.

Endocrine System: rare: goiter, hypothyroidism.

Hemic and Lymphatic System: rare: lymphadenopathy, leukopenia, petechia, anemia, thrombocytopenia, lymphocytosis, pancytopenia.

Metabolic and Nutritional Disorders: frequent: thirst; infrequent: dehydration, weight loss; rare: gout, SGOT increased, healing abnormal, acid phosphatase increased, SGPT increased, diabetes mellitus.

Musculoskeletal System: frequent: myasthenia, arthralgia; infrequent: arthritis, tenosynovitis; rare: pathological fracture, osteoporosis fracture, bone pain, myositis, tendon rupture, arthrosis, bursitis.

Nervous System: frequent: hypesthesia, apathy, depression, hypokinesia, vertigo, twitching, agitation, anxiety, amnesia, hyperkinesia, paresthesia; infrequent: ataxia, delirium, delusions, depersonalization, dyskinesia, extrapyramidal syndrome, libido increased, coordination abnormal, dysarthria,

hallucinations, manic reaction, neurosis, dystonia, hostility, reflexes increased, emotional lability, euphoria, paranoid reaction; rare: aphasia, nystagmus, akathisia, stupor, dementia, diplopia, drug dependence, paralysis, grand mal convulsion, hypotonia, myoclonus, psychotic depression, withdrawal syndrome.

Respiratory System: frequent: cough increased, sinusitis; infrequent: epistaxis, bronchitis, asthma, pneumonia; rare: asphyxia, laryngitis, pneumothorax, hiccup.

Skin and Appendages: frequent: pruritus, rash; infrequent: acne, exfoliative dermatitis, dry skin, herpes simplex, alopecia; rare: urticaria, herpes zoster, skin hypertrophy, seborrhea, skin ulcer.

Special Senses: infrequent: eye pain, abnormality of accommodation, conjunctivitis, deafness, keratoconjunctivitis, lacrimation disorder, glaucoma, hyperacusis, ear pain; rare: blepharitis, partial transitory deafness, otitis media, taste loss, parosmia.

Urogenital System: frequent: urinary tract infection; infrequent: kidney calculus, cystitis, dysuria, urinary incontinence, urinary retention, vaginitis, hematuria, breast pain, amenorrhea, dysmenorrhea, leukorrhea, impotence, rare: polyuria, urethritis, metrorrhagia, menorrhagia, abnormal ejaculation, breast engorgement, breast enlargement, urinary urgency.

DRUG ABUSE AND DEPENDENCE

Controlled Substance Class

REMERON™ (mirtazapine) Tablets are not a controlled substance.

Physical and Psychologic Dependence

REMERON™ (mirtazapine) has not been systematically studied in animals or humans for its potential for abuse, tolerance or physical dependence. While the clinical trials did not reveal any tendency for any drug-seeking behavior, these observations were not systematic and it is not possible to predict on the basis of this limited experience the extent to which a CNS-active drug will be misused, diverted and/or abused once marketed. Consequently, patients should be evaluated carefully for history of drug abuse, and such patients should

be observed closely for signs of mirtazapine misuse or abuse (e.g., development of tolerance, incrementations of dose, drug-seeking behavior).

OVERDOSAGE

Human Experience

There is very limited experience with REMERON™ (mirtazapine) overdose. In premarketing clinical studies, there were nine reports of mirtazapine overdose alone or in combination with other pharmacological agents. The only drug overdose death reported while taking REMERON™ (mirtazapine) Tablets was in combination with amitriptyline and chlorprohixene in a non-U.S. clinical study. Based on plasma levels, the REMERON™ dose taken was 30-45 mg, while plasma levels of amitriptyline and chlorprohixene were found to be at toxic levels. All other premarketing overdose cases resulted in full recovery. Signs and symptoms reported in association with overdose included disorientation, drowsiness, impaired memory, and tachycardia. There were no reports of ECG abnormalities, coma or convulsions following overdose with REMERON™ alone.

Overdose Management

Treatment should consist of those general measures employed in the management of overdose with any antidepressant. There are no specific antidotes for REMERON™. If the patient is unconscious, establish and maintain an airway to ensure adequate oxygenation and ventilation. Gastric evacuation either by the induction of emesis or lavage or both should be considered. Activated charcoal should also be considered in treatment of overdose. Cardiac and vital signs monitoring is recommended along with general symptomatic and supportive measures.

In managing overdosage, consider the possibility of multiple-drug involvement. The physician should consider contacting a poison control center for additional information on the treatment of any overdose.

DOSAGE AND ADMINISTRATION

Initial Treatment

The recommended starting dose for REMERON™ (mirtazapine) is 15

mg/day, administered in a single dose, preferably in the evening prior to sleep. In the controlled clinical trials establishing the antidepressant efficacy of Remeron, the effective dose range was generally 15-45 mg/day. While the relationship between dose and antidepressant response for REMERON™ has not been adequately explored, patients not responding to the initial 15 mg dose may benefit from dose increases up to a maximum of 45 mg/day. REMERON™ has an elimination half-life of approximately 20-40 hours, therefore, dose changes should not be made at intervals of less than one to two weeks in order to allow sufficient time for evaluation of the therapeutic response to a given dose.

Elderly and Patients with Renal or Hepatic Impairment

The clearance of mirtazapine is reduced in elderly patients and in patients with moderate to severe renal or hepatic impairment. Consequently, the prescriber should be aware that plasma mirtazapine levels may be increased in these patient groups compared to levels observed in younger adults without renal or hepatic impairment. (See Pharmacokinetics Subsection of CLINICAL PHARMACOLOGY).

Maintenance/Extended Treatment

There is no body of evidence available from controlled trials to indicate how long the depressed patient should be treated with Remeron. It is generally agreed, however, that pharmacological treatment for acute episodes of depression should continue for up to six months or longer. Whether the dose of antidepressant needed to induce remission is identical to the dose needed to maintain euthymia is unknown.

Switching Patients to or from a Monoamine Oxidase Inhibitor

At least 14 days should elapse between discontinuation of an MAOI and initiation of therapy with REMERON™. In addition, at least 14 days should be allowed after stopping REMERON™ before starting an MAOI.

HOW SUPPLIED

REMERON™ (mirtazapine) Tablets are supplied as:

15 mg Tablets - oval, scored, yellow, coated, with "Organon" embossed on one side and "TZ3" on the other side.

Bottles of 30 NDC# 0052-0105-30
Bottles of 100 NDC# 0052-0105-91
Bottles of 500 NDC# 0052-0105-95
Unit Dose, Box of 100 NDC# 0052-0105-90*
30 mg Tablets - oval, scored, red-brown, coated, with
"Organon" embossed on one side and "TZ5" on the other side.

Bottles of 30 NDC# 0052-0107-30
Bottles of 100 NDC# 0052-0107-91
Bottles of 500 NDC# 0052-0107-95
Unit Dose, Box of 100 NDC# 0052-0107-90
*Unit dose packs are provided as a blisterpack with 10 strips,
each of which contain 10 tablets.

Store at controlled Room Temperature
20°-25°C (68° - 77°F) [See USP]

Dispense in a tight, light resistant container.

Caution: Federal law prohibits dispensing without
prescription.

Doc LABMRTDP.AP1

DAVID

NDA 20-415

APR 19 1996

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

Dear Mr. Mayo:

Please refer to your pending New Drug Application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Remeron™ (Mirtazapine) 15 and 30 mg tablets.

We additionally acknowledge receipt of your response to an Agency approvable letter, including a safety update, in a submission dated March 15, 1996.

Reference is also made to a telephone conversation between Dr. Loan Tran, of your office, and Mr. Paul David, of this Agency, in which the Agency requested the following information (faxed to Dr. Tran on February 27, 1996) which was inadvertently omitted from our approvable letter dated January 26, 1996:

World Literature Update

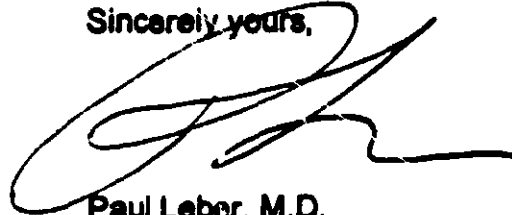
Prior to the approval of Remeron™, we require an updated report on the world's archival literature pertaining to the safety of Remeron™. This report should cover all relevant published papers, including clinical or preclinical data, that were not submitted with the original NDA or in subsequent amendments.

Additionally, we need your warrant that you have reviewed this literature systematically, and in detail, and that you have discovered no finding that would adversely affect conclusions about the safety of Remeron™. The report should also detail how the literature search was conducted, by whom (their credentials) and whether it relied on abstracts or full texts (including translations) of articles. The report should emphasize clinical data, but new findings in preclinical reports of potential significance should also be described. Should any report or finding be judged important, a copy (translated as required) should be submitted for our review.

We note that, although your March 15, 1996, response refers to a comprehensive literature search in reference to the safety update, you have not yet specifically responded to the above request for a literature update. Therefore, we are again requesting a world literature update. This update would need to involve a systematic literature search for all information pertaining to Remeron™.

Should you have any questions concerning this NDA, please contact Mr. Paul A. David, Project Manager, at (301) 594-2777.

Sincerely yours,

A large, stylized handwritten signature in black ink, likely belonging to Paul Leber, M.D. To the right of the signature, there is a handwritten date and initials: "4/12/90".

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

DAVID

APR 22 1996

NDA 20-415

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

Dear Mr. Mayo:

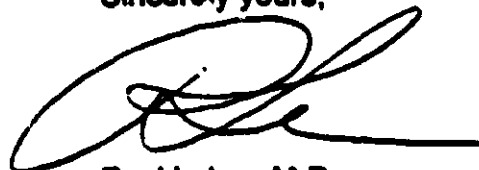
Please refer to your pending New Drug Application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Remeron™ (Mirtazapine) 15 and 30 mg tablets.

We additionally acknowledge receipt of your response to an Agency approvable letter, including a safety update, in a submission dated March 15, 1996.

Upon initial review of your response to the Agency's approvable letter, we noted that the Agency inadvertently omitted a request for foreign labeling as part of a regulatory status update. In addition, while the regulatory status update included in your March 15, 1996 amendment did note recent approval actions, it did not address the issue of negative actions. Consequently, we ask that you comment on any negative actions taken by foreign regulatory authorities with regard to mirtazapine. Please describe in detail any and all actions taken that have been negative, supplying a full explanation of the views of all parties and the resolution of the matter. In addition, we ask that you provide us any current foreign labeling for mirtazapine, along with English translations when needed.

Should you have any questions concerning this NDA, please contact Mr. Paul A. David, Project Manager, at (301) 594-2777.

Sincerely yours,



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

EXCLUSIVITY SUMMARY for NDA # 20-415 SUPPL # _____

Trade Name Remeron Generic Name Mirtazapine

Applicant Name Organon HFD- 120

Approval Date _____

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it an original NDA? YES ☒ / NO ☐ /

b) Is it an effectiveness supplement? YES ☐ / NO ☒ /

If yes, what type? (SE1, SE2, etc.) _____

- c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES ☒ / NO ☐ /

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES / ☒ / NO / ☐ /

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

5 years

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use?

YES / ☐ / NO / ☒ /

If yes, NDA # _____ Drug Name _____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES / ☐ / NO / ☒ /

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES / ☐ / NO / ☒ /

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____

NDA # _____

NDA # _____

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES / ☐ / NO / ☐ /

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____

NDA # _____

NDA # _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /___/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

- (a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /___/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

- (b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /___/

- (1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO?

YES /___/ NO /___/

If yes, explain: _____

- (2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /___/

If yes, explain: _____

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # _____

Investigation #2, Study # _____

Investigation #3, Study # _____

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

- a). For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study # _____

NDA # _____ Study # _____

NDA # _____ Study # _____

- b). For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study # _____

NDA # _____ Study # _____

NDA # _____ Study # _____

- c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #__, Study # _____

Investigation #__, Study # _____

Investigation #__, Study # _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

- a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1	!	
IND # _____ YES /___/	!	NO /___/ Explain: _____
	!	_____
Investigation #2	!	
IND # _____ YES /___/	!	NO /___/ Explain: _____
	!	_____

- (b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	!	
YES /___/ Explain _____	!	NO /___/ Explain _____
_____	!	_____
_____	!	_____

Investigation #2

YES /___/ Explain _____

NO /___/ Explain _____

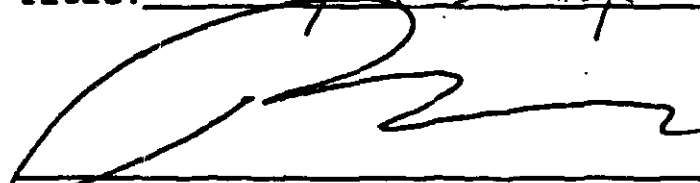
- (c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /___/

If yes, explain: _____


Signature
Title: Project Manager

10-18-95
Date


Signature of Division Director

10/18/95
Date

cc: Original NDA

Division File

HFD-85 Mary Ann Holovac

DRUG STUDIES IN PEDIATRIC PATIENTS
(To be completed for all NME's recommended for approval)

NDA # 20-415

Trade (generic) names Renuron (Mirtazapine)

Check any of the following that apply and explain, as necessary, on the next page:

- ☐ 1. A proposed claim in the draft labeling is directed toward a specific pediatric illness. The application contains adequate and well-controlled studies in pediatric patients to support that claim.
- ☐ 2. The draft labeling includes pediatric dosing information that is not based on adequate and well-controlled studies in children. The application contains a request under 21 CFR 210.58 or 314.126(c) for waiver of the requirement at 21 CFR 201.57(f) for A&WC studies in children.
- ☐ a. The application contains data showing that the course of the disease and the effects of the drug are sufficiently similar in adults and children to permit extrapolation of the data from adults to children. The waiver request should be granted and a statement to that effect is included in the action letter.
- ☐ b. The information included in the application does not adequately support the waiver request. The request should not be granted and a statement to that effect is included in the action letter. (Complete #3 or #4 below as appropriate.)
- ☒ 3. Pediatric studies (e.g., dose-finding, pharmacokinetic, adverse reaction, adequate and well-controlled for safety and efficacy) should be done after approval. The drug product has some potential for use in children, but there is no reason to expect early widespread pediatric use (because, for example, alternative drugs are available or the condition is uncommon in children).
- ☐ a. The applicant has committed to doing such studies as will be required.
- ☐ (1) Studies are ongoing.
- ☐ (2) Protocols have been submitted and approved.
- ☐ (3) Protocols have been submitted and are under review.
- ☐ (4) If no protocol has been submitted, on the next page explain the status of discussions.
- ☐ b. 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 do not need to be encouraged because the drug product has little potential for use in children.

☒ c. We will add for studies in approvable letter.

5. If none of the above apply, explain.

Explain, as necessary, the foregoing items:

cc: Orig MDA
 11-D- /Div File
 1A Action Package

10-14-95
Date

#447

REQUEST FOR TRADEMARK REVIEW

TO: Labeling and Nomenclature Committee
Attention: Ms. Yana Mille, Chair, (HFD-611: MPX II)

FROM: Division of Neuropharmacology HFD-120
Attention: Mr. Paul David Phone: 594-5530

DATE: June 7, 1995

SUBJECT: Request for Assessment of a Trademark for a Proposed Drug Product

Proposed Trademark: Remeron
Company Name: Organon

NDA/ANDA# 20-415

Established name, including dosage form: Mirtazapine Tablets 15
and 30 mg Tablets

Other trademarks by the same firm for companion products: N/A

Indications for Use (may be a summary if proposed statement is lengthy): Antidepressant Tetracyclic Class

Initial comments from the submitter: (concerns, observations, etc.)

The Division does not have any concerns or observations with the proposed Trademark. Please have your committee comment on the sponsor's proposed name.

Should you have any questions, please contact the Project Manager, Mr. Paul David, at 594-5530.

NOTE: Meetings of the Committee are scheduled for the 4th Tuesday of the month. Please submit this form at least one week ahead of the meeting. Responses will be as timely as possible.

Consult #447 (HFD-120)

REMERON

Mirtazapine Tablets 15 mg and 30 mg

A review revealed no names which sound like or look like the proposed name.

The Committee has no reason to find the proposed name unacceptable.

CDER Labeling and Nomenclature Committee

Yana Ruth Mills, Chair

7/9/95

COMPLETED

NDA 20-415

JUN 12 1995

Organon Inc.
Attention: Patrick J. Osinski
375 Mt. Pleasant Avenue
West Orange, New Jersey 07052

Dear Mr. Osinski:

We have completed our review of the manufacturing and controls and the environmental assessment sections of your new drug application for Remeron (Mirtazapine) Tablets dated January 26, 1995, and received January 30, 1995.

A summary of the manufacturing and controls and the environmental assessment deficiencies we have identified is provided below.

Manufacturing and Controls

Please note that our review does not encompass your amendment dated May 25, 1995. If you believe that any of the deficiencies listed below are answered by this amendment, please state so in your cover letter response.

1. You should provide evidence for the absence of polymorphic forms of the n.d.s. Such information was not found in your application.
2. Since a more efficient assay has been developed and used, you need to amend the n.d.s. specifications to substitute the new assay results should be provided for clinical batches as well as recent production batches. The Methods Validation packages need to be corrected to reflect the changes in the assay methods. Additionally, please send us a full copy of your revised Methods Validation packages.
3. The n.d.s. specifications should include a chirality test as part of the identity testing. We recognize that mirtazapine is a racemic compound but, since it does have a chiral center, such test is required. Determination of optical rotation is sufficient as such a test and we understand that it has already been developed to analyze two batches (R and V).
4. The n.d.s. specifications should include limits and tests for residual solvents.
5. Packaging-component testing data are required and should include FTIR identity testing.
6. You should provide your sampling plans for testing drug product batches.

7. It is not clear if the _____ used in the granulation procedure is the _____ for the _____. You need to identify the _____. Also, no description is provided for the _____.
8. What are your established reprocessing operations? Please note that we could not locate them in your submission.
9. You need to provide an update of the 3-month stability study on the proposed market formulations. The 3-month results and the provided supportive data do not support the proposed expiry date.

Environmental Assessment

1. Regarding Section 4, description of the proposed action:

a. Requested approval

The NDA number should be included in the description of the proposed action. The basis for the EA requirement should also be noted (e.g., "This EA has been submitted in accordance with 21 CFR 21.35a.").

b. Production locations

i. Proprietary intermediate(s)

It should be confirmed that any intermediates used in the manufacture of the drug substance are commercially available in the open marketplace. If proprietary intermediates are used, the manufacturing facility and information relating to that facility must be provided.

ii. Drug Substance

The full address of the facility should be provided.

iii. Finished Dosage Form

The full address of the facility should be provided.

c. **Expected locations of use (drug product)**

This information is not provided in the assessment. EA should indicate where product is expected to be used (e.g., in hospitals, clinics, or private homes) and whether use will be more prevalent in any particular geographic area.

d. **Disposal locations**

At the end of Section 7 of the EA, it is stated that unused, rejected or recalled product will be incinerated at the Essex County Resource Recovery Facility. This information should be provided in Section 4 of the EA along with the address and applicable permit information.

Confidential Appendix VII indicates that some of the product will be blister packed. Information regarding the disposal of PVC packaging materials is also needed if they are to be incinerated because of toxic emissions.

2. **Regarding Section 5, Identification of chemical substances that are the subject of the proposed action:**

The expected "standard excipients," if any, should be identified, or a confidential appendix containing the information should be referenced.

3. **Regarding Section 6, Introduction of substances into the environment: For the site(s) of production:**

a. **Controls (Air, Liquid Effluent, Solid):**

No mention is made of solid waste generation or disposal. If no solid waste is generated from the production processes, EA should so state.

b. **Compliance with federal, state and local emission requirements:**

Information confirming compliance with state and Federal regulations in the United States should be provided. Information confirming compliance with the Netherlands environmental laws was missing as attachment B in your recent resubmission.

c. **Effect of approval on compliance with current emissions requirements:**

EA should estimate for the US of the increase in emissions and waste generation that will result based on production projections and confirm that current permits will not be exceeded.

d. **Estimated expected emitted concentration/quantities:**

The calculation is based on a five year production projection divided by five (i.e., an average annual production rather than a maximum) and assumes that production will be equally distributed between the 15 and 30 mg dosages. EA should present a five year marketing plan for the drug products so that the maximum annual production figure can be used in the equation.

4. **Regarding Section 7, Fate of emitted substances in the environment:**

No information is provided in Section 7 of the EA regarding either the in vivo form of the drug substance or metabolites. Section 4.B states that mirtazapine "...is predominantly metabolized to 8-hydroxy analogues. Urine in patients contains conjugated 8-hydroxy analogues and a demethyl [sic] analogue (conjugated with glucuronic or sulfonic acid)." This information should be expanded upon in Section 7 of the EA. Any additional metabolites should be noted and the percentages of major metabolites provided. While it appears from the information provided that the major metabolites will behave in the environment similarly to the parent compound, this should be confirmed.

5. **Regarding Section 8, Environmental effects of released substances:**

The EA does not provide study results for photodegradation in soils. Neither does the EA provide results of toxicity tests for terrestrial species such as earthworms (EATAD 4.12). Microbial inhibition testing was conducted, and the minimum inhibitory concentration for test fungi, soil bacteria, ascomycete, and nitrogen fixing bacteria was greater than 292 mg/l, far exceeding the MEEC. This does not necessarily demonstrate, however, a lack of toxicity to terrestrial organisms.

It is noted in the present case that, due to its strong sorptive capacity and lack of biodegradability, all of the excreted drug substance (including that released to private septic systems), will eventually make its way to a POTW. Looking back to the information provided for the aquatic compartment, it is noted that the substance has a short half-life at all pH levels tested due to aquatic photodegradation. Exposure of the sorbed drug substance to this degradation process should occur in the POTW. Because of this, it may be unlikely that a significant quantity of the drug substance will enter the terrestrial compartment.

The validity of this logic will depend on a number of factors, including the effects of sorption on the efficiency of the aquatic photodegradation process.

The EA should more explicitly address the fate of the drug substance in the terrestrial compartment or explain why this is not relevant. If it cannot be adequately demonstrated that the substance will be degraded in the POTW, toxicity testing on appropriate terrestrial species should be carried out.

It should be kept in mind that the requirements of this section of the EA apply also to metabolites if it cannot be demonstrated that they will behave similarly to the parent compound due to chemical structure.

6. Regarding Section 9, Use of resources and energy:

a. Production:

Specific information should be provided regarding energy and water resources (and others if appropriate) associated with the production of the drug substance, manufacture of the drug product, and packaging processes. Information can be in the form of actual projected usage or as percentage increases/decreases over current use at each facility.

b. Effect on endangered/threatened species:

EA should discuss the presence, or absence of endangered or threatened species that might be impacted by activities (including accidental releases) associated with the drug substance production, product manufacture, or disposal facilities.

c. Effect on properties listed/eligible for national register of historic places:

See comments under Section 9.b above.

7. Regarding Section 10, Mitigation measures:

There is no specific information in the EA to suggest the "highly regulated and controlled" nature of the activity. Only passing reference is made to the National Nuisance Act and the Water Pollution Act in Section 6 of the EA, and no information is provided regarding activities at the packaging and distribution site in the United States. Please cite various procedures to mitigate release, such as:

- Adherence to specific Federal, State and local regulations
- Equipment systems used to prevent emissions levels from exceeding established limits
- Spill and accidental release control plans
- Occupational health and safety program
- Annual training regarding hazardous materials, personal protective equipment and production equipment and SOP's and personal safety practices

Also, if materials will be destroyed only by high temperature incineration, this should be listed as a mitigating measure.

8. Regarding Section 12, List of preparers, & their qualifications (expertise, experience, professional disciplines) and consultants:

EA should also indicate the qualifications of the individual identified (e.g., expertise, experience, professional disciplines).

9. Regarding Section 13, Certification:

Section should also provide signature and date.

10. Regarding Section 14, References:

The EA should list all documents used in the conduct of the assessment. Each of the confidential attachments on physical testing, for example, carries a reference to the FDA EATAD. These references and any other relevant documents should be listed in this section of the assessment.

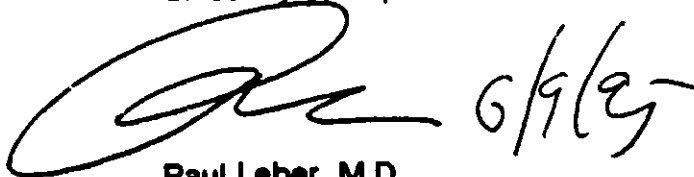
11. Regarding Section 15, Appendices:

This section of the EA should contain a listing of all appendices and/or attachments to the EA. These items are currently listed on page ii of the Table of Contents.

The data and information that will be submitted in your reply to this summary should be provided in two submissions (one for the manufacturing and controls, and the other for the environmental assessment) and within thirty days in order to avoid a possible extension of the review period. If some of the information is not available when you respond, please state this in your cover letter.

Should you have any questions concerning this NDA, please contact Mr. Paul David, Regulatory Management Officer, at (301) 443-3504.

Sincerely yours,



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

NDA 20-415

JUN 28 1995

Organon Inc.
Attention: Patrick J. Osinski
375 Mt. Pleasant Avenue
West Orange, New Jersey 07052

Dear Mr. Osinski:

Please refer to your New Drug Application (NDA) submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for Remeron® (Mirtazapine) tablets.

Reference is also made to an Agency letter dated June 12, 1995, informing you of the manufacturing and controls deficiencies in your application.

We additionally refer to your amendment dated May 25, 1995, providing for additional chemistry information.

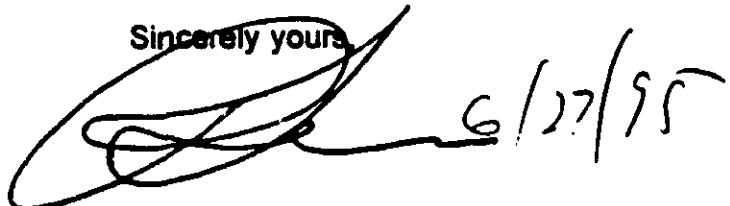
We have completed our review of your amendment, and it has adequately responded to the following deficiencies that were brought to your attention in our June 12, 1995 Agency letter.

1. Description of the new assay for the n.d.s. and its inclusion in the n.d.s. specifications (Partial response to Deficiency 2).
2. Proper identification of the and other equipments used in the manufacturing process of the drug product and definition of the breaking strength unit (response to Deficiency 7).

The remaining deficiencies in our letter dated June 12, 1995, are still outstanding and were not addressed in this amendment. In addition, we request that you specify the regulatory method you will use as the assay for the drug product specifications. The methods you choose as "alternate" should not be part of the specifications. Also, we require the available up-to-date production-scale batch records and analytical data to support the modified manufacturing process and specifications.

Should you have any questions concerning these comments, please contact Mr. Paul David, Regulatory Management Officer, at (301) 443-3504.

Sincerely yours,



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

NDA 20-413

JUL 11 1994

Organon Inc.
Attention: Roy W. Dodsworth
Director, Regulatory Affairs
375 Mt. Pleasant Avenue
West Orange, New Jersey 07052

Dear Mr. Dodsworth:

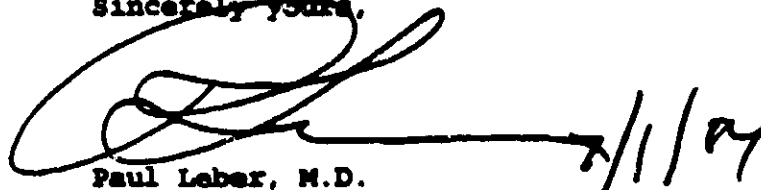
We acknowledge receipt of your communication dated June 27, 1994, requesting withdrawal of your pending new drug application (NDA) for Remeron® (Mirtazapine) tablets.

In compliance with your request and as provided for in 21 CFR 314.65, the application is considered to be withdrawn as of the date of our receipt of your request for withdrawal, June 27, 1994.

This withdrawal does not prejudice and future resubmission. You may request that the information contained in the withdrawn application be considered in conjunction with any resubmission.

Should you have any questions concerning this NDA, please contact Mr. Paul David, Regulatory Management Officer, at (301) 594-2777.

Sincerely yours,

A handwritten signature in black ink, appearing to be "P. Leber", followed by a date "7/11/94" written vertically.

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

NDA 20-415

Organon Inc.
Attention: Roy W. Dodsworth
Director, Regulatory Affairs
375 Mt. Pleasant Avenue
West Orange, New Jersey 07052

MAY 23 1994

Dear Mr. Dodsworth:

We have received your New Drug Application submitted pursuant to section 505(b)(1) of the Federal Food, Drug and Cosmetic Act for the following:

Name of Drug Product:	Remeron (Mirtazapine) Tablets
Date of Application:	April 29, 1994
Date of Receipt:	April 29, 1994
Our Reference Number:	20-415

Unless we find the application not acceptable for filing, the filing date will be June 28, 1994.

Please begin any communications concerning this application by citing the NDA number listed above. Should you have any questions concerning this NDA, please contact Mr. Paul David, Regulatory Management Officer, at (301) 443-3504.

Sincerely yours,

 5/12/94

John S. Purvis
Supervisory Consumer Safety Officer
Division of Neuropharmacological
Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

**DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS
MEDICAL OFFICER'S CONSULTING REVIEW**

NDA: 20-415

SPONSOR: Organon Inc.
375 Mt. Pleasant Ave., West Orange, NJ 07052

DATE OF REQUEST: 6 October 1995, by Paul David, HFD-120

DATE OF RECEIPT: 8 October 1995

ASSIGNED FOR REVIEW: 11 October 1995

DRUG: Mirtazapine (Remeron®) tablets, 15 and 30 mg

ROUTE OF ADMINISTRATION: Oral, preferably h.s.

PROPOSED INDICATIONS: Treatment of depression

MATERIAL REVIEWED: Medical Officer's (J. Balian, M.D.) review, hematology consultation (L. Talarico, M.D., HFD-180), individual patient summaries, Advisory Briefing Document, all of which were received 11 October 1995.

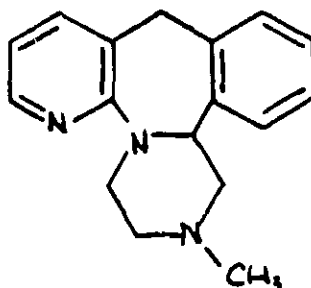
REVIEWER: John R. Senior, M.D./ 12 October 1995

Background, Introduction

The request for consultation was initiated by Mr. Paul David, project manager of NDA 20-415 and Dr. John Balian, medical reviewer, and forwarded on 6 October 1995 to the Division of Gastrointestinal and Coagulation Drug Projects (DGCDP), HFD-180, for consultation regarding the incidence of hepatic dysfunction tests observed during the clinical trials. A consultation about the observed cases of neutropenia had been prepared by Dr. Lilia Talarico, of DGCDP, and forwarded 22 September, noting a 0.1% (3/2796) incidence rate of severe neutropenia and 0.3% reversible neutropenia after discontinuation of Org3770 (mirtazapine). She advised that the hematological risk had to be evaluated in the context of overall efficacy and other risks of the drug. In further discussion with Dr. Talarico, the parallel question of the hepatic risks of the drug was raised, and it was decided to seek an opinion as to whether scheduled hepatic monitoring should be included in the labeling. The issue was of some urgency because of the planned Psychopharmacologic Drugs Advisory Committee meeting set for 16 October 1995.

The drug is a novel piperazinoazepine tetracyclic compound with centrally active presynaptic α_2 adrenergic receptor antagonistic properties that increase noradrenergic neurotransmission, and also central serotonin modulating properties by interaction with 5-HT₂ and 5-HT₁ receptors that may explain its antidepressant effects. Its S(+) enantiomer blocks α_2 and 5-HT₂ receptors, and the R(-) enantiomer blocks 5-HT₁ receptors. The drug also is a centrally active H₁ receptor antagonist, an action that may explain its initial sedative effects, and also has anxiolytic properties.

Mirtazapine is almost insoluble in water, but is appreciably soluble in methanol, toluene, diethyl ether, hexane, and other organic solvents. It is prepared as a racemic mixture, both enantiomers of which are active but at different receptor sites. Its structure lacks the basic side chain that is said to be responsible for the unwanted anticholinergic effects of tricyclic antidepressants.



$C_{17}H_{19}N_3$
m.w. 265.36

mirtazapine (ORG 3770, Remeron®)

The acute toxicity of both enantiomers are similar, in animal studies reported by the sponsor. Like many other tertiary amines, it is rapidly absorbed after oral administration, reaching peak plasma levels within 45 minutes in rats and in 1.0-1.5 hours in dogs. Its metabolism is principally hepatic, via demethylation to an active metabolite, and N(2)-oxidation and 8-hydroxylation and conjugation to inactive metabolites. The half-time of elimination is relatively short (2 to 6 hours), so little accumulation of active compounds (but some retention of radioactivity in the melanin of skin, brain, and eyes in rats) occurs with repeated daily dosing. Some induction of hepatic enzymes by high doses was observed in the animal studies. No acute hepatic toxicity was seen, but sub-chronic doses of 40 and 120 mg/kg/day for 13 weeks to rats resulted in mild hepatic cell hypertrophy without hepatic functional disturbances or hepatotoxicity. Chronic administration of 2.5 and 15 mg/kg/day for one year to beagles caused no untoward effects, but 80 mg/kg/day caused mild increases in serum alkaline phosphatase and alanine aminotransferase activities within the first six months, and liver enlargement and hepatic cell hypertrophy possibly indicating enzyme induction without morphological changes indicating hepatotoxicity after six or twelve months. A slight increase in hepatic tumors was seen in mice given 200 mg/kg/day for 18 months, thought to be unique to the mouse and not expected in humans.

Studies in human volunteers showed that daily doses of up to 80 mg may be tolerated by healthy men, although some showed drowsiness, hypotension, faintness, dizziness, or elevated serum levels of transaminases, all reversible upon discontinuation of the drug. Orally administered ORG 3770 was rapidly absorbed, reaching peak plasma concentrations in about two hours, with about 50% absolute bioavailability, with little effect of food in the stomach. The elimination half-time was 20 to 40 hours, with decreases in clearance in patients with hepatic or renal dysfunction, and slower clearance in healthy females than males. The metabolism was similar to that seen in animals, with cytochrome P-450 isoenzyme 2D6 (CYP2D6) mainly responsible for the 8-hydroxylation, with some contribution by CYP1A2; the same cytochrome CYP1A2, but also CYP2D6, CPA, and CYP2B6

were responsible for the N-demethylation, while CYP1A2, CPA, and CYP2C9 were active in forming the N-oxide of the drug. Because of its high degree of expression in the liver, CYP3A, especially CPA, may be most important in formation of both the N-demethyl and N-oxide metabolites. It was not stated which cytochrome P-450 isozymes were induced by long-term administration of ORG 3770.

Clinical Evidence of Possible Hepatotoxicity

As summarized by the Medical Reviewer, there were 26 of 2796 (0.9%) patients treated with mirtazapine during the clinical trials who were prematurely discontinued from study or who had a serious event related to increases in serum levels of alkaline phosphatase (AP), gamma-glutamyl transferase (GGT), alanine aminotransferase (ALT, also known as SGPT), aspartate aminotransferase (AST, also known as SGOT), or lactate dehydrogenase (LDH). Among patients randomized to placebo, there were 2 of 605 (0.3%) and in those taking active control compounds such as amitriptyline, trazodone, clomipramine, diazepam, doxepin, and maprotiline, 2 of 1171 (0.2%). Concomitant use of alcohol seems related to some of these events. In none of the 8 cases of intentional or accidental overdoses involving mirtazapine, alone or in combination with other drugs, was there any indication of hepatotoxicity. Among the 12 patients who died after receiving at least some doses of mirtazapine, none were associated with hepatic abnormalities (9 suicides, 2 acute myocardial infarctions, 1 acute cholecystitis with shock). In the U.S. controlled studies involving 1242 patients, a very high dropout rate of almost 50 % was observed, attributed to lack of efficacy in 43% of those on placebo (178), and to adverse reactions in 60% of those on trazodone (15), in 55% of those on amitriptyline (122), and in 36% of those on mirtazapine (278). In patients taking mirtazapine who dropped out, somnolence was the main complaint, with nausea a distant second, both significantly more than in the placebo groups, but none because of evidently liver-related symptoms. Serious events occurred in about 3% of those taking mirtazapine, comparable to 3.3% in those taking other antidepressant agents. One patient (#1051), a 37-year-old white woman, stopped mirtazapine after 162 days, at which time she was taking 60 mg/day because of further elevations in serum GGT beyond her moderately elevated pre-treatment levels, associated with low-grade, variable new elevations of ALT and LDH and great increase in the previous slight elevation of her AST. After 159 days, while taking 45 mg/day of mirtazapine her serum AST was 1380, ALT 280, GGT 560, LDH 1900, and the mirtazapine was stopped on day 162. Seven days later she had a massive gastrointestinal bleeding episode from a large gastric ulcer, lapsed into coma in hospital, regained consciousness but suffered anoxic brain damage and died in a nursing facility several months later. Further information was denied by her family.

In most of the cases in which premature discontinuation or a serious event occurred in patients taking mirtazapine, the enzyme elevations were modest, transient, and often resolved even though the drug was continued. In no case was documented histologic abnormality found in association with the enzyme elevations, nor evidence of hepatic dysfunction as indicated by jaundice or significant bilirubin elevations reported.

An apparent causal relationship between mirtazapine and elevated serum enzyme levels was cited by the Medical Reviewer, modest and transient in most cases, often resolving spontaneously even with drug discontinuation, but always reversible upon discontinuation of the drug without leaving any sequelae to indicate hepatic dysfunction. The incidence of these events appeared comparable to that in patients taking other ("active control") antidepressant agents, but greater than in patients on placebo.

Comments and Recommendations

Occurrence of sporadic elevations in serum activities of liver-related enzymes during controlled clinical trials is common, and has often been observed with other neurotropic and other types of new drugs under investigation. As experience has taught us, however, this does not necessarily assure the hepatic safety of such new agents. Elevated enzymes do not always indicate hepatic inflammation (hepatitis), but may result from leakage of intracellular enzymes from hepatocytes under influence of metabolizing foreign substances such as new drugs. In many people, metabolic adaptation to the new drug occurs, and the enzyme leakage stops, without further cellular dysfunction, injury, or tissue change. For example, on the order of 40% of people starting isoniazid may show transaminase elevations initially, but most adapt and the elevations disappear despite continuing the drug; in a few, however, the elevations persist, increase, and may be associated with histologic hepatitis, clinical liver dysfunction, hepatic necrosis, liver failure and death.

The so-called "idiosyncratic" cases of hepatotoxicity may be of sufficient rarity that trial of even several thousand patients fail to detect events that may occur in 1:5,000 or 1:10,000 patients. When the drug is approved for clinical use, however, it is taken by tens or hundreds of thousands of patients, and such rare events become manifest. It is also true that during clinical trials, the use of other drugs, alcohol, and pre-existing liver disease are causes for exclusion; this is not true after approval of the drug for use for some other medical problem, in this case, depression. There is also no way to prevent patients for whom an antidepressant is prescribed from drinking alcohol, from taking acetaminophen for colds or various aches, from using other drugs that they or their doctors may think necessary, whether over-the-counter or by prescription. The mild, minor, transient, and sporadic transaminase elevations observed in these clinical studies do not suggest hepatotoxicity (in the sense of a predictable, dose-related, hepatocyte-necrotizing or cholestasis-inducing drug), but do suggest that alertness to detect idiosyncratic responses may be in order. It does not matter whether those "idiosyncratic" responses are due to genetic differences, altered immune system effects, the addition of another drug or food or medicinal agent of some sort — the observed abnormalities represent a warning that they may occur. Surveillance is therefore appropriate.

It is my recommendation that monthly ALT levels be required in the labeling for three months after starting mirtazapine, and quarterly thereafter. In the event of a reported abnormality, the ALT elevation should be confirmed, and buttressed by other measures such as AST, AP, GGT, and total bilirubin done every few days while the drug is continued to see if the levels are constant or rising, in which case the drug should be stopped. In such cases, consultation with a gastroenterologist or

hepatologist may be considered, and liver biopsy done if clinical evidence of liver dysfunction is found. A registry of reports of such cases should also be considered, which may establish more accurately the incidence of significant cases of hepatotoxicity. If the enzyme elevations are transient and harmless, that also will be of interest, and will go far toward establishing the hepatic safety of the new drug.

Although this represents a modest burden of cost and effort, the alternative of not doing it may cause history to be repeated and reports of serious hepatic necrosis and death to follow marketing and wide use of the new agents, as has been true for several recently introduced agents that then had to be withdrawn.

<i>John R. Senior MD</i>	<i>12 October 1995</i>
John R. Senior, M.D.	date
Medical Reviewer, DGCDP	

cc:

NDA 20,415

HFD-180

HFD-180/SFredd

HFD-180/JSenior

HFD-181/CSO

HFD-120

HFD-120/PLeber

HFD-120/JBalian

HFD-121/CSO

MED\C20415510.0JS

APPENDIX 8.5.2.1.3
LIST OF PATIENTS WITH CLINICALLY SIGNIFICANT
INCREASES IN LIVER ENZYMES

Study	Patient	Age	Sex	Mirt. mg/d	Days	Comments
Serious Cases						
003-010	1051	37	F	40	162	PT* due to liver enzyme elevations (GGT 560, SGPT 280, SGOT 1380, and LDH 1900). 4 days after stopping Org 3770, the patient's enzymes had decreased close to normal levels, but patient suffered massive GI bleeding from a large gastric ulcer and was hospitalized in a coma. She regained consciousness but suffered anoxic brain damage; she was placed in a home and died several months later.
Symptomatic Cases						
003-003	29	29	M	20	13	PT due to symptomatic (diarrhea, fever, and nausea) chemical hepatitis. Lab findings showed leukopenia and clinically significantly elevated liver enzymes (ALT 46, AST 31 at baseline and 506 and 351 at day 16, respectively). The WBC and the biochemical hepatitis (elevated liver enzymes) returned to normal limits by 21 and 42 days after stopping the drug, respectively. A hepatitis panel was negative.
> 5 Fold Enzyme Elevation From Baseline						
003-010	283	30	M	37.5	16	PT because of elevated SGOT (175) and SGPT (431). The elevations began at day 8 (15 mg/day) and reached clinically significant levels by day 14 at a dose of 30 mg/day. The investigator, not aware of the laboratory results, again increased the dose of Org 3770 to 37.5 mg/day for two days before the patient was discontinued from the study. The liver enzyme levels increased for 7 more days after the drug had been discontinued (study day 21), but were normal by day 45. The only concomitant medication was Tylenol 500 mg for headache.
003-010	137	44	M	60	238	PT. From study day 59 until discontinuation, the patient's liver enzymes were found to be significantly high (maximum values for SGPT of 181 and for GGT of 826).

Liver Enzyme units are IU/L.

PT* = premature termination.

APPENDIX 8.5.2.1.3 (CONTINUED)
LIST OF PATIENTS WITH CLINICALLY SIGNIFICANT
INCREASES IN LIVER ENZYMES

Study	Patient	Age	Sex	Mirt. mg/day	Days	Comments
> 5 Fold Enzyme Elevation From Baseline (cont)						
85031	172	31	M	64	17	PT due to elevated LDH (329), SGOT (119), and SGPT (404).
003-010	219	30	M	15	203	PT for increased liver enzymes (SGOT: 278 IU/L and SGPT: 106 IU/L). He also had a clinically significant elevation in SGPT (150 IU/L) on study day 14, at a dose of 7.5 mg/day. This patient also had below-the-normal-range counts of WBCs and neutrophils (see hematology)
	392	35	M		279	PT for marked elevation of liver enzymes (LDH 1130, SGPT 1255, and SGOT 1815). A blood sample taken three days later showed liver enzymes somewhat elevated but returning to normal. Evaluation ruled out a viral infection. The patient admitted to heavy alcohol intake the prior week. In the nine months prior to this event, he had only two episodes of slightly elevated GGT levels.
003-010	842	26	M	15	21	PT because of clinically significant increases in liver enzymes (SGPT 203, SGOT 89). At day 39 the patient was <u>rechallenged</u> after the enzyme levels had decreased (still borderline high), the enzyme levels increased more modestly, but the patient was continued on the study. On day 152 he had normal levels, but they fluctuated until end of study (day 403) when it was normal.

APPENDIX 8.5.2.1.3 (CONTINUED)
LIST OF PATIENTS WITH CLINICALLY SIGNIFICANT
INCREASES IN LIVER ENZYMES

Study	Patient	Age	Sex	Mirt. mg/day	Days	Comments
3-5 Fold Enzyme Elevation From Baseline						
003-010	858	32	M	37.5	34	Patient with history of cocaine and alcohol abuse in the past, had baseline levels of GGT (115), SGPT (73), SGOT (31), AP (109). The study was interrupted at day 34 while the patient was taking Org 3770 37.5 mg/day, because of clinically significant increases in liver enzymes (GGT 271, SGPT 144, SGOT 81, and AP 138). At day 75 the patient was <u>rechallenged</u> after the enzyme levels had decreased (still borderline high), the enzyme levels increased again, but the patient was continued until end of study (day 328). One month after termination the patient had a liver biopsy which was consistent with chronic persistent hepatitis. In this reviewer's opinion the patient had baseline chronic persistent hepatitis that was exacerbated with treatment, including rechallenge.
003-010	1062	42	M		110	PT due to increases in liver enzyme values (SGPT 150). He experienced increased but fluctuating levels from day 14 on. A month after discontinuation he had normal levels.
The other cases with less dramatic enzyme elevations leading to premature terminations in the Org 3770 treated groups are: patient #s 117, 340, 342, 363, 365, 379, 615, 638, 706, 724, 803 (in Study 003-010), 103 (in Study 003-008), 2 (in Study 003-021), 14 (in Study 003-003), 96 (in Study 003-028). Also with minor elevation, but listed under serious adverse events, is patient #104 from Study 84072.						

APPENDIX 8.5.2.1.3 (CONTINUED)
LIST OF PATIENTS WITH CLINICALLY SIGNIFICANT
INCREASES IN LIVER ENZYMES

Study	Patient	Age	Sex	Mirt. mg/day	Days	Comments
Prematurely Terminated Cases Under Other Adverse Events But Of Interest To The Hepatotoxicity Review						
003-010	936	59	M	45	406	PT due to increased anxiety and alcohol use which caused an increase in liver enzyme values (SGPT 119).
003-010	648	58	F		150	PT because of lack of efficacy. At screening, the patient's GGT level was clinically significantly high. GGT levels remained high and on study day 59, GGT levels worsened to 262 and SGPT was elevated to 88. During the remainder of the study, sporadic high levels of these enzymes were observed. The patient drank alcohol "socially."
003-010	837	40	M	30	31	Patient lost to follow-up. At baseline the patient had borderline high increases in liver enzymes (SGPT 72). At day 31 the SGPT was 169.
003-010)	908	43	F	15	28	Patient had her treatment interrupted at 4 weeks, because of clinically significant increases in liver enzymes (SGPT 148). A month later the patient was <u>re-challenged</u> after the enzyme levels had decreased and this time there were no increases.
In this category also fall other cases with less dramatic enzyme elevations: patients # 170, 202, 224, 255, 664 (from Study 003-010).						
The 2 placebo premature termination cases include one (patient #74, study 003-003) with minimal elevation of SGOT and SGPT (46 and 64 IU/L, respectively), while the other case (patient #69, study 003-023) at day 21 of therapy had Alkaline phosphatase levels of 158, LDH of 408, SGOT of 118 and SGPT of 195. The 2 active control patients include: (i) Patient #42, (Study 003-023), a 62-year-old-female on trazodone experienced liver enzyme elevation (SGOT 205, SGPT 369, LDH 256 and alkaline Phosphatase 252) at last assessment day of the 6 week study. The levels were normal 21 days after stopping treatment; (ii) Patient #163, (Study 85004), a 36-year-old-male on meprotiline, presented with nausea and vomiting on day 12 of treatment. On day 13 his SGPT was 265 and SGOT 145. The drug was withdrawn and levels normalized.						

REVIEW AND EVALUATION OF CLINICAL DATA

Application Information

NDA # 20-415

Sponsor: Organon Inc.

Clock Date January 30, 1995

Drug Name

Generic Name: Mirtazapine

Proposed Trade Name: Remeron™

Drug Characterization

Pharmacological Category: Antidepressant

Proposed Indication: Treatment of depression

NDA Classification: 1-S

Dosage Forms, Strengths, and Routes of Administration:
Oral tablets in 15 and 30 milligram strengths.

Reviewer Information

Clinical Reviewer: John Dikran Balian, M.D.

Review Completion Date: October 19, 1995

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1.0 Material Utilized in Review

1.1 Material from NDA

Appendix 1.1.1 gives the list of specific items reviewed in compiling this document. Safety issues were evaluated on the basis of the integrated safety summary; selective case report forms and narrative summaries.

Appendix 1.1.2 gives the list of the CRFs (case report forms) specifically examined by me. Many more patient narratives were actually examined. Also examined were the reviews of the internal consultants: Statistics (Joy Mele), Biopharmaceutics (Safa Ibrahim), Pharmacology (Steven Sparenborg), Hematology (Dr. Lilia Talarico) and Gastroenterology (Dr. John Senior). The comments and recommendations of the external hematology consultant, Dr. Lewis Weintraub of Boston University made during several informal discussions, a teleconference and at the PDAC meeting on October 16, 1995 were also taken into consideration.

1.2 Material from IND

The following division files were consulted for this review: (i) IND # Organon's commercial IND for mirtazapine; (ii) IND individual investigator sponsored IND for mirtazapine (6-azamianserin); and (iii) IND #

2.0 Background

2.1 Indication

There is a large array of specific and effective antidepressant drugs currently available: the first-generation medications include the MAOIs and the TCAs; and the second-generation include the SSRIs (fluoxetine, paroxetine, sertraline), venlafaxine, nefazodone, bupropion, trazodone, and maprotiline.

Despite extreme differences in chemical structures, pharmacokinetics, and pharmacodynamics, no currently available compound has been shown to be clearly superior in efficacy. However several substances have disadvantages which limit their clinical usefulness: these include weight gain, cardiotoxicity, dietary restrictions, proconvulsant properties, toxicity in overdose, sleep disturbance, and anti-cholinergic side effects (dry mouth, double vision, drowsiness, and ataxia) (Hindmarch and J. Kerr. Behavioral toxicity of antidepressants with particular reference to meclobemide. Psychopharmacology 1992;106:S 49-S 55.).

Mirtazapine, a tetracyclic compound, belongs to the piperazino-azepine group and is not chemically related to the tricyclic

antidepressants. It is a centrally acting presynaptic alpha₂ adrenergic antagonist, which in animal studies has been shown to increase noradrenergic neurotransmission. Mirtazapine is an enantiomeric compound. The (+) enantiomer blocks alpha₂ and the 5-HT₂ receptors, and the (-) enantiomer blocks the 5-HT₁ receptor. Through the modulation of this serotonin function via interaction with the 5-HT₁ and the 5-HT₂ receptors it is believed that mirtazapine exerts its antidepressant effect. Mirtazapine also possesses antihistaminic (H₁) activity, explaining its sedative effects, but lacks the basic side chain believed to be responsible for the anti-cholinergic side effects. In introducing mirtazapine, the sponsor is attempting to find an effective drug treatment with minimal side effects. The NDA sponsor requests mirtazapine indication for the treatment of depression and with a special mention that mirtazapine has been shown to reduce anxiety, which is often associated with depressive disorders.

2.2 Related INDs and NDAs

Organon's commercial IND for mirtazapine is IND # _____ first submitted 7/82. There is one investigator sponsored IND, by Max Fink.

2.3 Administrative History

Regarding IND _____ a depression study, there is scanty information in the division file. The IND was submitted at 5/79 under the drug name Org 3770 and generic name 6-azamianserin. It was inactivated by the sponsor on 6/82.

IND # _____ Organon's commercial IND for mirtazapine as an antidepressant, was reviewed on 7/22/82. The IND was originally placed on clinical hold because it lacked a protocol, and more studies on dogs were requested to study prostatic atrophy seen in the animals. At time of submission two small clinical studies had been performed in Germany at low doses (0.5mg), where there was lowering of BP.

A number of serious adverse events were reported to the IND: pancytopenia, neutropenia, agranulocytosis, and thrombocytopenia. Due to the hematologic adverse events weekly WBC monitoring was instituted in the IND studies.

The original NDA was submitted on 4/29/94. This submission was

withdrawn by the sponsor on 6/27/94 after the FDA informed Organon that the submission lacked certain critical clinical data, in particular case report forms from overseas studies. Subsequently, a pre-NDA meeting was held on 7/22/94 to discuss these concerns. The NDA was re-submitted on Jan. 30, 1995.

2.4 Directions for use

In the proposed labeling, the only specified contraindication is hypersensitivity to the drug or its components

There are two warnings in the proposed labeling: (i) Agranulocytosis: In premarketing clinical trials, three (one with Sjogren's Syndrome) out of 2,796 patients treated with mirtazapine tablets developed severe neutropenia ($ANC < 1,500$), two of which developed clinical agranulocytosis. In all cases, the patients recovered after the drug was stopped. If a patient develops a sore throat, fever, stomatitis or other signs of infection, along with a low WBC count, treatment should be discontinued and the patient closely monitored. The sponsor is not proposing routine blood counts. (ii) MAO Inhibitors: since there are no human data to establish the safety of combining an MAOI with mirtazapine, it is recommended that mirtazapine not be used in combination with an MAOI, or within 14 days of initiating or discontinuing therapy with an MAOI.

The sponsor's proposed labeling includes precautions regarding the following: somnolence, dizziness, increased appetite/weight gain, cholesterol/triglycerides, transaminase elevations, activation of mania/hypomania, seizures, suicide, and overdose.

The sponsor's labeling also provides the following recommendations:

Pregnancy: The drug is classified as pregnancy Category B and it should be used during pregnancy only if clearly needed.

Teratogenic Effects: There are no adequate and well controlled studies in pregnant women.

Nursing Mothers: It is not known whether mirtazapine is secreted in human milk; caution should be exercised when mirtazapine is administered to nursing women.

Pediatric Use: Safety and effectiveness in children have not been established.

Geriatric Use: Pharmacokinetic studies revealed a decreased clearance in the elderly, especially elderly females. Care should be exercised in titration to higher doses.

Drug interactions: The proposed labeling indicates that there has

been evaluation of the potential for interaction of some drugs with mirtazapine: (i) Alcohol and Diazepam: The impairment of mental and motor skills produced by mirtazapine have been shown to be additive with those produced by alcohol and diazepam. Accordingly, patients should be advised to avoid alcohol, diazepam, and other similar drugs while taking mirtazapine. (ii) Drugs Affecting Hepatic Metabolism: The metabolism and pharmacokinetics of mirtazapine may be affected by the induction or inhibition of drug metabolizing enzymes. (iii) Drugs Metabolized by Cytochrome P450 IID6: Concomitant use of mirtazapine with drugs metabolized by cytochrome P450 IID6 has not been formally studied. Therefore, co-administration of mirtazapine, with other drugs that are metabolized by this isoenzyme, including certain antidepressants (e.g., nortriptyline, amitriptyline, desipramine and fluoxetine), phenothiazines (e.g., thioridazine) and Type 1C antiarrhythmics (e.g., propafenone, flecainide and encainide), or that inhibit this enzyme (e.g., quinidine), should be considered with care. (iv) Drugs Bound to Plasma Protein: Because mirtazapine is non-specifically bound to plasma proteins (85%), care should be exercised when Mirtazapine, is co-administered to a patient who may be receiving another drug which is highly protein bound.

Dosage and Administration: The recommended initial dosage is 15 mg daily preferably administered at night. Patients not responding to the initial dosage may be titrated as needed to a maximum of 45 mg/day. Mirtazapine has an elimination half-life of approximately 20-40 hours, hence any dose escalation should not occur in intervals of less than two weeks.

2.5 Foreign Marketing

Mirtazapine has been marketed in the Netherlands since Sept. 30, 1994 and has received registration approval in Finland, Austria and Peru. It also has received provisional approval by the CPMP.

3.0 Chemistry

The chemistry of mirtazapine has been reviewed separately. There are no outstanding chemistry issues of clinical relevance.

4.0 Animal Pharmacology

The animal pharmacology is reviewed separately and only a brief summary is presented here.

Nonclinical pharmacology studies show that mirtazapine has moderately weak antagonist properties at central and peripheral α_1 adrenoreceptors (hence, it caused orthostatic hypotension). It also possesses α_2 , 5HT₂, and 5HT₁ antagonistic activity leading to its putative antidepressant and antianxiety activities. Mirtazapine also interacts with H₁ (histamine) receptors, hence

its antihistaminic property of somnolence. It is devoid of anticholinergic activity.

Acute Toxicity: Oral LD₅₀ in male Swiss mice was 830 mg/kg (760-940) after 24 hours and 810 mg/kg (720-1010) after 7 days. In females the oral LD₅₀ was 720 mg/kg (620-850) after both 24 hours and 7 days. In male and female Wistar rats the oral LD₅₀ was 490 mg/kg (427-524) after 24 hours and 320 mg/kg (240-430) after 7 days. The acute toxicity of mirtazapine and its enantiomers were comparable. Signs of acute toxicity included motor incoordination, reduced activity, ptosis, twitches, abnormally slow respiration, and piloerection. These symptoms reached their peak within two hours and gradually disappeared during the same day. Gross anatomy revealed no morphological changes.

In multidose toxicity studies for 13 weeks in Wistar rats at 10 mg/kg there were no findings, but at 40 and 120 mg/kg mirtazapine induced transient clinical signs of weight loss, increases in thyroid (males only) and adrenal gland (females only) weights, and mild renal and hepatic tissue changes. All findings reversed during a four week observation period. In Beagle dogs there were increased liver weights and behavioral changes at 20 mg/kg, and at 80 mg/kg slight body weight loss in males, decreased RBC parameters, decreased testicular weight associated with reduced spermatogenesis and decreased epididymal weights and spermatozoal contents. A significant decrease in prostatic weight in all drug-treated animals and one control male was observed.

Chronic toxicity: One year studies in Sprague Dawley rats with daily doses of 2.5, 20, and 120 mg/kg and Beagle dogs with 2.5, 15, and 80 mg/kg had no additional toxicity findings.

Carcinogenicity: In an 18 month study in mice at 2, 20, and 200 mg/kg/day, the incidence of masses/nodules in the livers of mid- to high-dose males was notably higher compared to the low dose and control groups. Microscopic analysis of liver showed a significant increase in hepatocellular neoplasm in males at high doses (these were benign adenomas). In rats given 2, 20, and 60 mg/kg, benign or malignant neoplasms occurred in various organs, most notably in the pituitary glands, mammary glands, adrenal glands, skin, thyroid, and liver. Only the thyroid follicular cell neoplasm incidence was statistically significantly higher in the high dose males.

Mutagenicity: Mirtazapine did not demonstrate mutagenic potential in any of the four in vitro tests (the Ames, the sister Chromatid test, unscheduled DNA synthesis in Hela S3 cells, and gene mutation test in Chinese hamster) or in one in vivo test (Micronucleus test).

Impairment of fertility: No adverse effects on mating behavior and pregnancy were observed in male rats given 100 mg/kg for two

weeks prior to and during the mating period, and female rats treated with 100 mg/kg for 7 days prior to, during the mating period, and up to day 6 of pregnancy. In a separate study male rats received 2.5, 15, and 100 mg/kg for nine weeks prior to and during mating; female rats received the same doses for 14 days prior to, during, and up to day 7 of pregnancy or through pregnancy and lactation. Males and females in same dose groups were mated. General condition, mating performance, and fertility were not adversely affected, and no increased embryotoxic or teratogenic effects were observed in mirtazapine treated animals. In the high dose group, increased neonatal mortality within 24 hours post partum and depressed paternal body weight were observed. Subsequent development of the F1 generation was not adversely affected.

The potential embryotoxicity was tested in rats and rabbits with doses of 100 mg/kg during organogenesis, or 2.5, 15, and 100 mg/kg from day 6 to 17 in pregnant rats, and there was no induction of any teratogenicity. At the highest doses, depressed maternal body weights, food consumption, and fetal weight as well as significantly increased gestation length and increased post-implantation loss were observed. There were no adverse effects in the F1 generation. In the rabbit study no maternal toxicity or embryonic effects were found.

Peri- and post-natal study: In treatments from day 17 of pregnancy through day 28 of lactation in rats with doses of 100 mg/kg there was increased neonatal mortality within 24 hours and significantly decreased body weight of the F1. No adverse effects on the estrous cycle pattern, mating and pregnancy performance, pre- and post-implantation loss or physical and behavioral development of the F1 generation were observed in any dose group.

Mirtazapine is transferrable via the placenta and milk (in small quantities) in rats.

5.0 Description of clinical data sources

5.1 Primary development program

5.1.1 Study type and Design/Patient Enumeration

All but one (Non-US Study #86017) of the studies in the development program were completed well before the time of the original submission (4/94) of this NDA. At the time of resubmission (1/95), the enrollment and treatment phase of study (#86017) was completed but the data were not analyzed, hence study #86017 is not part of the integrated safety database. The primary data reviewed and presented here come from studies completed before 12/93 that will have no additional information forthcoming.

Since the resubmission of the NDA (1/95), 5 more studies (#s E1490, E1527, E1546, 22506, and 22507) were initiated. A 120 Day Safety Update Report, submitted by the sponsor on 7/28/95, deals with the 5 new studies, Study #86017 and the marketing of the drug in Netherlands. All serious adverse events pertaining to these studies have been reported and are included in my review, with clear identification and separation from the integrated database.

A brief summary of the exposure data for the 6 non-integrated database studies and the postmarketing data (surveillance report received 9/13/95) follows:

1. E1490 (completed) is a double-blind, placebo-controlled, 19-day study with 6 patients enrolled in the Org 3770 arm and 2 in the placebo;
2. E1527 is a double-blind, active-controlled, 6-week and 6-month extension study with 60 patients planned for enrollment in the Org 3770 and fluoxetine groups (by the date of this reported, 29 randomly enrolled);
3. E1546 (completed) is a 3-way-crossover (Org 3770, mianserin and placebo) study, 15-days for each arm and 18 patients;
4. 22506 is a double-blind, active-controlled, 6-week and 12-month extension study with 15 patients planned for enrollment in intravenously administered Org 3770 and clomipramine groups (by the date of this reported, 11 randomly enrolled);
5. 22507 is a double-blind, active-controlled, 6-week and 6-month extension study with 15 patients planned for enrollment in intravenously administered Org 3770 and maprotiline groups (by the date of this reported, 9 randomly enrolled);
6. 86017 (completed) is a double-blind, active-controlled, 6-week study with 53 and 54 patients enrolled in the Org 3770 and imipramine groups, respectively.

Estimated mirtazapine exposure (patients receiving at least one dose of Org 3770) in the 6 non-integrated database studies is 98 patients.

The Spontaneous Reporting System of the Postmarketing Surveillance Data in the Netherlands, from the time of introduction into the market (Sept. 94) until August 95 was submitted on 9/13/95. As reported by the sponsor, the extent of use during this period, estimated by sales figures and expressed in Defined Daily Doses (DDD) of 30 mg/day, reaches 393,165 DDDs

(or, 1077 patient-years). There were 23 adverse events reported; none were classified serious, but three were overdoses (to be discussed in section 8.5.10).

Appendix 5.1.1 lists the table summary of all studies with a brief description of each. Tables 5.1.1.1 (Phase I) and 5.1.1.2 (Phase II-III) enumerate the participants in the various phases of the sponsor's development program for mirtazapine.

**TABLE 5.1.1.1
SUMMARY OF ALL STUDIES
PHASE I (CLINICAL PHARMACOLOGY STUDIES)**

	Org 3770	Placebo	Amitriptyline	Diazepam
Single Dose				
U.S. Study	20	0	0	0
Non-U.S. Studies	156	54	12	12
Total	176	54	12	12
Multiple Dose				
U.S. Studies	70	0	0	0
Non-U.S. Studies	104	33	0	0
Total	174	33	0	0
Sub-Total	350	87	12	12

**TABLE 5.1.1.2
SUMMARY OF ALL
PHASE 2 AND 3 STUDIES**

	Org 3770	Placebo	Amitrip- tyline	Clomi- pramine	Diaze- pam	Doxepin	Mapro- tiline	Trazo- done
Short-Term Controlled Studies								
Fixed Dose Total	160	42						
Flexible Dose Total	1218	452	607	87	47	80	82	149
Short-Term Controlled Total	1378	494	607	87	47	80	82	149
Long-Term Controlled Studies¹								
U.S. Studies²								
Switchers	127	0	59			0		
Non- Switchers	94	66	86			0		
Non-U.S. All Non- Switchers	55	46	0			8		
Long-Term Controlled Total ¹	127	0	59	0	0	0	0	
Uncontrolled Studies								
Short-Term Uncontrolled	294							
Long-Term Uncontrolled	737							
Total	1031							
Controlled and Uncontrolled Total	2536	494	666	87	47	80	82	149
Nondepression Studies	180	70	0	0	50	0	0	0
Grand Total ⁴	2716	564	666	87	97	80	82	149

¹ Long-term studies were extensions of short-term studies. No new patients were enrolled in the long-term phase.

² Based on U.S. placebo controlled Studies 003-004, 003-005 (20 Org 3770 and 9 placebo patients), extensions of short-term Studies 003-002 and 003-003) and active and placebo controlled Studies 003-025, 003-026, 003-027, and 003-028 (extensions of short-term Studies 003-020, 021, 022 and 024 respectively). All four studies used amitriptyline as the active control.

Switchers are patients who switched treatment in the long-term phase after a one-week washout period (placebo to Org 3770 - 77 patients, amitriptyline to Org 3770 - 50 patients, and Org 3770 to amitriptyline - 59 patients). Non-switchers are patients who continued in the long-term studies under the same treatment group.

³ Only switchers are included in the total for long-term controlled studies, because they were exposed to a different treatment group than they were exposed to in the short-term phase.

⁴ The total does not include 84 patients from ongoing non-U.S. 86017 study with Org 3770 and imipramine. In addition, 2 patients who received compassionate use Org 3770 (in a non-U.S. program) are not included in the total.

A brief overview of the number of subjects receiving any treatment in Phase II-III clinical trials worldwide is as follows:

Drug	# of Patients	Patient Years of Exposure*	
		N*	Pt. Yrs.
Mirtazapine	2796	2425	671.7
Placebo	605	494	71.4
Amitriptyline	666	615	158.5
All Active			
Controls**	1161	977	195.2

*The N for patient years of exposure is less than the actual number exposed, because no exposure data was available for the remainder. The patient year is the duration of exposure equivalent to one patient taking the drug for one year, or 2 patients taking the drug for six months.

**Amitriptyline was the primary active control used, others included: trazodone, clomipramine, diazepam, doxepin, and maprotiline.

The mirtazapine NDA integrated safety summary was the main resource used to review the safety of this drug. The integrated summary of safety database includes data from all clinical pharmacology, efficacy, and safety studies conducted worldwide. A total of 350 patients exposed to mirtazapine provided data for the integrated Phase I safety database and 2796 patients exposed to mirtazapine provided data for the integrated Phase II-III safety database. While 2716 patients provided data for the integrated Phase II-III database (as reflected in Table 5.1.1B), 80 patients from study 84008 were treated with enantiomers of mirtazapine and are not included in this table (any adverse events among these 80 patients are considered). There are an additional 84 subject in an ongoing European study; these 84 are not part of the review and do not comprise any part of the numbers given above (any serious adverse events among these 84 patients are considered). The sponsor will continue sending reports of serious adverse drug events from the ongoing study, as required.

5.1.2 Demographics

Appendix 5.1.2.1 represents the demographic information of the US studies in the integrated Phase II-III safety data set. The mirtazapine treated subjects were predominantly white (> 94%); 41% were male and 59% female, with an average age of approximately 43 (range 18-88). The demographics for the placebo and the active groups are similar to the mirtazapine group. Appendix 5.1.2.2 gives a pooled dataset (US and Non-US). Table 5.1.2.1 represents the pooled data for the distribution of elderly patients (≥ 65 years of age):

Table 5.1.2.1

	Remeron	Placebo	Amit	Clomip	Diaz	Maprot	Trazod
Females	133	20	67	8	5	6	10
Males	57	9	13	0	0	0	3
Total	190	29	80	8	5	6	13

5.1.3 Extent of Exposure (dose/duration)

Table 5.1.3.1 represents the pooled data for duration of exposure to mirtazapine alone, by modal dose for all studies (US and Non-US).

TABLE 5.1.3.1
DURATION OF EXPOSURE BY MODAL DOSE:
ALL U.S. and NON-U.S. STUDIES (PHASE II-III)

Modal Dose (mg)	Duration of Exposure									Total (%)
	Days		Weeks					Years		
	1	2-7	1-4	4-8	8-16	16-28	28-52	1-2	>2	
Org 3770										
≤ 7.5	20	38	46	91	10	11	14	5	0	235 (9.7)
9 - 19	4	52	97	174	25	38	14	12	1	417 (17.2)
20 - 45	0	23	166	565	84	110	99	100	8	1155 (47.7)
> 45	0	0	38	376	40	39	68	55	1	617 (25.5)
Total (%)	24 (1)	113 (4.7)	347 (14)	1206 (49.8)	159 (6.6)	198 (8.2)	195 (8.0)	172 (7.1)	10 (0.4)	2424

Appendix 5.1.3.1 represents the same pooled data as Table 5.1.3.1, for duration of exposure by modal dose for all studies (US and Non-US), but it includes all active controls as well. A total of 2424 patients exposed to mirtazapine are included in this analysis; due to absence of data on the remaining patients (all coming from Non-US studies) they are not included in this data set. Almost all the studies were dose escalation studies and the majority were 6 week studies followed by possible extensions of treatment. The largest number of patients received between 20-45 mg of mirtazapine, for 4-8 weeks. In terms of the proposed daily dose of 15 mg or 30 mg, an overwhelming majority (> 90%) in the dataset received modal dosages > 7.5 mg, and approximately 48% received modal daily dosages in excess of 20-45 mg. These parameters are true for the mean dose exposure as well.

Appendix 5.1.3.2 represents the non-pooled data for duration of exposure in patient years for the different study types (US and Non-US). For all patients for whom data exists (N=2425) the exposure in patient years for mirtazapine is 671.7. Appendices 5.1.3.3 and 5.1.3.4 show the pooled data for mean and maximum dose exposure, respectively. The difference in the two Ns given (in the text, the tables and the appendices) N=2425 for exposure in patient years and N=2424 for exposure by dose, is due to the availability of data on duration of exposure in one patient but not dose amount.

5.2 Secondary Sources

5.2.1 Other Studies and Compassionate Use

One patient received humanitarian treatment in U.S. Study 003-500, after participating in 003-002, and its extension 003-004. Two patients were exposed in a non-U.S. compassionate use program in the U.K. and their data are not included. Aside from the ongoing European study, there are no published reports or other data that are not included in the integrated summary (this was confirmed by sponsor in a telephone conversation on 4/20/95).

5.2.2 Postmarketing experience

Mirtazapine has been marketed in the Netherlands since Sept. 30, 1994. On 9/13/95 the company submitted the "Postmarketing Surveillance Data From Spontaneous Reporting System." There were 11 Spontaneous Reports with 23 adverse events (none were serious) in this submission, and additionally there were 3 overdose cases. Exposure data is covered in section 5.1.1. Specific cases, such as overdoses or other adverse events are discussed in the appropriate sections.

5.2.3 Literature

As part of the NDA, the sponsor has furnished an exhaustive

bibliography as reference. This was consulted in the preparation of the review.

6.0 Summary of Human Pharmacokinetics

The following is a brief summary of the pharmacokinetics of orally administered mirtazapine.

With single or multiple doses of mirtazapine bioavailability is approximately 50%. The presence or absence of food in the stomach has no effect on the rate or extent of absorption. Peak plasma concentrations are reached at about 2 hours after dosing, and plasma levels are linear over a dose range of 30 to 80 mg. The time to peak plasma concentration is independent of dose. The half-life of elimination of mirtazapine is approximately 20-40 hours, with females of all-ages exhibiting significantly longer elimination half-lives than males (see Table 6.1). These differences result in higher area-under-the-curve (AUC) for females compared to males. Elderly subjects had a significantly larger AUC than younger subjects.

TABLE 6.1
 $t_{1/2}$ (mean $\pm$ SD)*

Group	Single Dose	Multiple Dose
Adult male N=9	21.7 $\pm$ 4.2	22.1 $\pm$ 3.7
Adult female N=9	37.7 $\pm$ 13.3	35.4 $\pm$ 13.7
Elderly male N=8	32.2 $\pm$ 15.4	31.1 $\pm$ 15.1
Elderly female N=8	40.6 $\pm$ 12.8	39.0 $\pm$ 10.8

* expressed in hours.

The elimination half-life of mirtazapine was increased 40% in hepatically impaired subjects as compared to patients with normal hepatic function; this effect on elimination resulted in a 57% increase in AUC and a 33% decrease in clearance.

Mirtazapine is an enantiomeric compound. The (-) enantiomer has an elimination half-life that is approximately twice as long and achieves plasma levels that are three times as high as that of the (+) enantiomer. The question arises as to which enantiomer provides more prominent activity in vivo?

Mirtazapine is extensively metabolized via the P450 enzyme pathway and its major pathways of biotransformation are

demethylation and oxidation followed by conjugation. From in vitro studies, it was determined that mirtazapine is a substrate of four enzymes: CYP1A2, CYP2C9, CYP2D6 and CYP3A. From these preliminary studies it is not possible to determine the principal pathway (between CYP2D6 and CYP1A2). An analysis of the data by Dr. Ibrahim suggests that poor metabolizers of CYP2D6 will probably not experience accumulation of the parent compound. There are no inhibition studies on record, but data shown by the sponsor at the PDAC meeting on Oct. 16, 1995 indicates there is no strong inhibition of the enzymes by Remeron.

The demethyl metabolite is pharmacologically active and appears to have the same pharmacokinetic profile as the parent compound. The metabolites are eliminated via urine (75%) and feces (15%); approximately 90% of this elimination occurs within the first 72-96 hours. Renal impairment may result in significantly higher plasma levels.

Mirtazapine is approximately 85% bound to plasma proteins over a concentration range of 10 to 1000 ng/mL. Binding appears to be both nonspecific and reversible. No displacement studies have been done.

The sponsor performed one US study to explore the interaction of mirtazapine with food:

Study # 003-012 was an open-label, randomized, single dose, 2-way cross-over mirtazapine and food interaction study. The study was designed to compare the bioavailability of Org 3770 (15 mg) in fasting and fed states in 20 healthy volunteers. C_{max} , t_{max} and AUC were not significantly different in the fasting and fed states.

7.0 Efficacy Findings

7.1 Overview of Studies Pertinent to Efficacy

The mirtazapine NDA comprises of 47 Phase 2 and 3 clinical trials, of which 44 were intended for the most part to explore the antidepressant efficacy and 3 for antianxiety efficacy. Table 7.1.1 presents the 32 controlled trials from the 44 studies exploring the antidepressant efficacy of Org 3770:

Table 7.1.1
Controlled Efficacy Trials*

Study Design	US Studies	Non-US Studies
Placebo and Active-Controlled Short-term	5	1
Placebo-Controlled Short-term	3	5
Active-Controlled Short-term	0	9
Placebo and Active-Controlled Long-term	4	0
Placebo-Controlled Long-term	2	0
Active-Controlled Long-term	0	3

*Includes initiated and completed studies only.

The 12 studies not listed in table 7.1.1 were short or long term open label studies.

Reviews of the studies considered crucial to determine the efficacy of the drug are presented below. These 11 include 9 short term placebo-controlled studies, one fixed dose study, and a study analyzing the efficacy of the individual enantiomers of mirtazapine.

The long term studies are not presented in the review, because they were either (i)not properly designed: they were extensions of short term studies where clinical judgment was used in the selection process and no true randomization occurred; (ii)not placebo controlled; (iii)too small in sample size; or (iv)uncontrolled.

There were 3 fixed dose studies performed by the sponsor to analyze the dose-response relationship of mirtazapine. Of these

only one (#003-008; review follows) was placebo controlled and had a large enough sample size for proper consideration; 85002 was not placebo controlled and 84050 was prematurely terminated (due to the investigator's untimely death).

In preparation of the efficacy review frequent consultations were held with Joy Mele, M.S. (Mathematical Statistician) of the Biometrics division to allow for a full coverage of the issues and to avoid duplication. Ms. Mele's review was consulted as well. An example of the varied approaches of the clinical and statistical reviews is in the presentations of the premature terminations. The sponsor provided tables for reasons of premature terminations that are divided into multiple categories (e.g. lack of efficacy, lack of efficacy/adverse event, drug related adverse event, non-drug related, patient improvement). In her summary, Ms. Mele combined patients reporting lack of efficacy as a reason for dropout, while I combined patients reporting adverse events as a reason for dropout. Also, it should be noted that my review contains the appendices as provided by the sponsor, while Ms. Mele analyzed the data herself. The minor differences seen, in particular regarding the LOCF at endpoint are due to the company's usage of a window period (as requested by me) for an observation to be included in the analysis, while Ms. Mele analyzed all available data points.

7.2 Summary of Studies Pertinent to Efficacy

7.2.1 Study 003-002, Duration (Feb. '84- April '85)

7.2.1.1 Investigator and Location

The principle investigator was James L. Claghorn, M.D. of Clinical Research Associates in Houston, Texas.

7.2.1.2 Study Plan

Objective

The objective of this study was to assess the safety and efficacy of Org 3770 and placebo in the treatment of depression.

Population

Inclusion Criteria:

- A diagnosis of Major Depressive Disorder (DSM III criteria).
- Score on the HAM D-17 of at least 18 on day 0.
- Ages between 18 and 65 years old (females either surgically sterile or postmenopausal).
- Good physical health and no significant medical history and abnormal laboratory values.

-In-patients for four weeks.

Exclusion Criteria:

-A history of a primary diagnosis of

- schizophrenia or other psychosis.
- anxiety disorder
- adjustment disorder
- dysthymic or cyclothymic disorder
- atypical depressive disorder.
- known suicidal tendency.

-Heavy smokers (15 cigarettes or equivalent per day) or users of alcohol during the study.

-Treatment with ECT within 3 months of day 0.

-Patients on neuroleptics, MAO inhibitors, other anti-depressants, stimulants, appetite suppressors or other psychotropic drugs within seven days of day 0.

-Concomitant therapy with any CNS active drug, except for a night time sedative (1 gram of chloral hydrate for night-time sedation).

Planned Study Conduct/Dosing Plan

This was a six week, double-blind, placebo controlled study, with random allocation of 45 patients to each of the two treatment groups (Org 4419 or placebo). Patients were drug free for the 7 days prior to the initiation of the study.

The dose range was 5-35 mg/day. During the first week of treatment the dose was fixed at 10 mg/day, thereafter titration was at the investigator's discretion. The dose was administered in the evening.

Efficacy/Safety Assessments

The assessments of efficacy were done weekly as follows:

Hamilton Psychiatric Rating Scale for Depression (HAM-D 21), Montgomery-Asberg Depression Rating Scale (MADRS) and Clinical Global Impression (CGI) at days 0, 7, 21, 35 and 42.

Safety assessments and the days on which the assessments were done were as follows:

Laboratory (chemistry, hematology and urinalysis) and ECG: Screening, days 21 and 42; Vital Signs: Days 0, 7, 14, 21, 28, 35 and 42; and Physical Exam (PE): Days 0 and 42.

Analysis Plan

The sponsor designated a set of efficacy parameters a priori for the analysis plan: CGI, MADRS and HAM-D. To compare the drug and

placebo a Student-test (or an appropriate non-parametric equivalent) was to be used. The level of significance for the resulting two-sided tests was to be $\alpha=0.05$.

In addition to rating scales, the patient dropout rates at each week were to be investigated. The acceptability for inclusion in the efficacy analysis of a patient with major protocol violations was to be determined on an individual basis. To protect against the introduction of bias, these decisions were to be made before breaking the blind, whenever possible.

The analysis plan in the protocol for this study was followed by the sponsor, but this division requested a different format: mean change analysis of the intent to treat group using both the observed case analysis and the last observation carried forward. The results presented in this synopsis present pair-wise comparisons (using the Wilcoxon Rank Sum Test and a one-way analysis of variance) of the active treatments against placebo.

7.2.1.3 Study Conduct/Outcome

Patient Disposition

The number and percentage of patients who completed the study are shown in Table 7.2.1.3.1. The number and percentage of patients who discontinued prematurely are shown in Table 7.2.1.3.2. There were increased number of dropouts in the placebo group (40%) due to lack of efficacy as compared to Org 3770 (18%).

TABLE 7.2.1.3.1
U.S. STUDY 003-002
PATIENT COMPLETION RATES

Treatment Group	Total Patients Randomized	Intent-to-Treat Sample Number ^a	Number of Patients Completing Week ^a											
			1		2		3		4		5		6	
			Patients		Patients		Patients		Patients		Patients		Patients	
			N	%	N	%	N	%	N	%	N	%	N	%
Org 3770	45	44	42	95	42	95	37	84	36	82	33	75	26	59
Placebo	45	44	42	95	37	84	34	77	32	73	22	50	19	43

^a Patients who received assigned medication and had one or more efficacy assessments.
Includes patients having efficacy data within 3 days of the scheduled visit.

TABLE 7.2.1.3.2
U.S. STUDY 003-002
NUMBER AND PERCENT OF PATIENTS DISCONTINUING TREATMENT BY REASON AND WEEK

Reason for Termination	Week 1		Week 2		Week 3		Week 4		Week 5		Week 6	
	Org 3770	Plac	Org 3770	Plac	Org 3770	Plac	Org 3770	Plac	Org 3770	Plac	Org 3770	Plac
	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)
Lack of Efficacy				1/44 (2.3)		2/41 (4.9)		3/38 (7.9)	4/39 (10.3)	10/34 (29.4)	4/35 (11.4)	2/22 (9.1)
Adverse Event	1/45 (2.2)		1/44 (2.3)		2/43 (4.7)		1/40 (2.5)	1/38 (2.6)		1/34 (5.9)	1/34 (2.9)	
Lost-to-Follow-Up		1/45 (2.2)		2/44 (4.5)	1/43 (2.3)	1/41 (2.4)					1/35 (2.9)	

Patients who "discontinue treatment" in an interval are those patients whose last efficacy visit occurred in the previous interval.
N(%) is based on intent-to-treat efficacy data set.
% is percentage of all patients in a treatment group who did not discontinue in an earlier interval.

Demographic Characteristics

Appendix 7.2.1.3.1 presents the demographic characteristics of the patients enrolled. There were more females enrolled in the Org 3770 arm (55% to placebo's 48%), but there was not a large difference in the groups with respect to mean age.

Baseline Severity of Illness

Appendix 7.2.1.3.2 presents the Baseline Severity of Illness. There was no statistically significant difference in the HAM-D 21 and the CGI, but the placebo group had a statistically

significantly higher MADRS score.

Dosing Information

Appendix 7.2.1.3.3 presents the Dosing Information for the study. The mean dose at week 1 was 9.7 mg/day, then successively increased to 20.7 mg/day at week 6.

Concomitant Medications

33 (31%) of Org 3770 and 42% of placebo patients received concomitant medications including: chloral hydrate, decongestants and analgesics.

Efficacy Results

For this review, efficacy was analyzed for the HAM D-21 Item scale, the HAM D Item #1 (mood), the MADRS and the CGI. These results are presented in Appendices 7.2.1.3.4-8. For each of the four parameters, the observed case analysis is presented for each visit, and the last observation carried forward analysis for the same parameter is presented for endpoint.

Org 3770 was statistically significantly more effective than placebo in relieving the symptoms of depression on all four measures of efficacy in weeks 1 through 4 for the observed cases (OC) and for all timepoints and at endpoint for the LOCF (although only endpoint shown in the table). For the observed cases in weeks 5 and 6, Org 3770 was not statistically significantly more effective than placebo in relieving the symptoms of depression.

Conclusion

This study demonstrates the efficacy of mirtazapine in the treatment of major depression. Org 3770 was statistically significantly more effective than placebo in relieving the symptoms of depression when evaluating the LOCF of the above mentioned parameters. Although no statistical significance is noted at weeks 5 and 6 for the OC, the mirtazapine patients continue to show greater mean decreases in the total scores of the efficacy variables than the placebo patients. An explanation for the differences between the OC and LOCF at weeks 5 and 6 is the large number of dropouts for lack of efficacy between the placebo group (40%) and the mirtazapine group (18%).

7.2.2 Study 003-003, Duration (June '84- Dec. '85)

7.2.2.1 Investigator and Location.

The principle investigator was John P. Feighner, M.D. of Feighner

Research Institute Encinitas, CA.

7.2.2.2 Study Plan

Same as Study 003-002.

7.2.2.3 Study Conduct/Outcome

Patient Disposition

The number and percentage of patients who completed the study are shown in Table 7.2.2.3.1. The number and percentage of patients who discontinued prematurely are shown in Table 7.2.2.3.2.

TABLE 7.2.2.3.1
U.S. STUDY 003-003
PATIENT COMPLETION RATES

Treatment Group	Total Patients Randomized	Intent-to-Treat Sample Number ^a	Number of Patients Completing Week ^b											
			1		2		3		4		5		6	
			Patients		Patients		Patients		Patients		Patients		Patients	
			N	%	N	%	N	%	N	%	N	%	N	%
Org 3770	45	45	44	98	36	80	34	76	35	78	31	69	27	60
Placebo	45	45	44	98	42	93	37	82	35	78	30	67	24	53

^a Patients who received assigned medication and had one or more efficacy assessments.

^b Includes patients having efficacy data within 3 days of the scheduled visit.

TABLE 7.2.2.3.2
U.S. STUDY 003-003
NUMBER AND PERCENT OF PATIENTS DISCONTINUING TREATMENT BY REASON AND WEEK

Reason for Termination	Week 1		Week 2		Week 3		Week 4		Week 5		Week 6	
	Org 3770	Plac	Org 3770	Plac	Org 3770	Plac	Org 3770	Plac	Org 3770	Plac	Org 3770	Plac
	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)
Lack of Efficacy			1/45 (2.2)					2/40 (5.0)	1/35 (2.9)	1/35 (2.9)	2/32 (6.3)	
Adverse Event			6/45 (13.3)	3/45 (6.7)	2/38 (5.3)	1/42 (2.4)		1/40 (2.5)		2/35 (5.7)	1/32 (3.1)	5/32 (15.6)
Patient Improvement								1/40 (2.5)				
Lost-to-Follow-Up						1/42 (2.4)		1/40 (2.5)	1/35 (2.9)			

Patients who "discontinue treatment" in an interval are those patients whose last efficacy visit occurred in the previous interval.

N(%) is based on intent-to-treat efficacy data set.

% is percentage of all patients in a treatment group who did not discontinue in an earlier interval.

Demographic Characteristics

Appendix 7.2.2.3.1 presents the demographic characteristics of the patients enrolled. There were more males enrolled in the Org 3770 arm (43%) but more females in the placebo 67%, but there were no differences in the groups with respect to mean age.

Baseline Severity of Illness

Appendix 7.2.2.3.2 presents the Baseline Severity of Illness. There were no statistically significant differences.

Dosing Information

Appendix 7.2.2.3.3 presents the Dosing Information for the study. The mean dose at week 1 was 9.9 mg/day then successively increased to 26.6 mg/day at week 6.

Concomitant Medications

24 (53%) of Org 3770 and 60% of placebo patients received concomitant medications, notably chloral hydrate and analgesics.

Efficacy Results

For this review, efficacy was analyzed for the HAM D-21 Item scale, the HAM D Item #1 (mood), the MADRS and the GAS. These results are presented in Appendices 7.2.2.3.4-8. For each of the four parameters, the observed case analysis is presented for each visit, and the analysis of the last observation carried forward for the same parameter is presented for endpoint.

Org 3770 was not more effective than placebo in relieving the symptoms of depression on any of the four measures of efficacy at any timepoint, except for week 4 for MADRS using a one-way analysis of variance.

Conclusion

Based on the analysis of efficacy results in this study Org 3770 was not superior to placebo in the treatment of major depression. The design and conduct of this study possessed all the qualities that were present in 003-002, and yet it failed to show any efficacy. Without the presence of an active control, it is difficult to clinically determine whether this study is failed or negative.

7.2.3 Study 003-008, Duration (June '88 - Nov. '90)

7.2.3.1 Investigator and Location

The principle investigator was James L. Claghorn, M.D. of Clinical Research Associates in Houston, Texas.

7.2.3.2 Study Plan

Objective

The primary objective of this study was to determine the optimal Org 3770 dose for the average moderate to severely depressed outpatient, and to assess the safety and efficacy of Org 3770 and placebo in the treatment of depression.

Population

Inclusion and Exclusion Criteria:

Same as Study 003-002.

Planned Study Conduct/Dosing Plan

This was the placebo-controlled, fixed-dose study in the development of this NDA. Study 003-008 was a six week, double-blind, placebo controlled study, with random allocation of 30 patients to each of the five treatment groups (Org 3770 5mg, 15mg, 30mg and 60mg or placebo). Patients were drug free for the 7 days prior to the initiation of the study. There was a dose titration period of 14 days, then a maintenance period of 28 days.

Table 7.2.3.2.1 shows the daily dose schedule for each of the five treatment groups.

TABLE 7.2.3.2.1
U.S. STUDY 003-008
DAILY DOSE FOR EACH DOSE GROUP

Dose Group	Study Day					
	1-2	3-4	5-7	8-10	11-14	15-42
Placebo	0	0	0	0	0	0
5 mg	5 mg	5 mg	5 mg	5 mg	5 mg	5 mg
15 mg	5 mg	10 mg	15 mg	15 mg	15 mg	15 mg
30 mg	5 mg	10 mg	20 mg	30 mg	30 mg	30 mg
60 mg	5 mg	10 mg	20 mg	30 mg	45 mg	60 mg

Efficacy/Safety Assessments

Efficacy Assessments were same as in Study 003-002.

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Safety assessments and the days on which the assessments were done were as follows:

Laboratory (chemistry, hematology and urinalysis): Screen, baseline, weeks 2, 4 and 6 (protocol was amended in 6/89 to add laboratory evaluations at weeks 1,3, and 5); ECG: weeks 2, 4 and 6; Vital Signs: Baseline and weeks 1-6; pregnancy tests: Baseline and weeks 4 and 6; and PE: Screen, baseline and week 6.

Analysis Plan

The sponsor designated a set of efficacy parameters a priori for the analysis plan: CGI, MADRS and HAM-D. To compare the different doses of the drug and placebo a Student-test (or an appropriate non-parametric equivalent) was to be used. The level of significance for the resulting two-sided tests was to be $\alpha=0.05$.

Further details of the analysis plan were as in study 003-002.

7.2.3.3 Study Conduct/Outcome

Patient Disposition

The number and percentage of patients who completed the study are shown in Table 7.2.3.3.2. The number and percentage of patients who discontinued prematurely are shown in Appendix 7.2.3.3.1.

TABLE 7.2.3.3.2
U.S. STUDY 003-008
PATIENT COMPLETION RATES

Treatment Group	Total Patients Randomized	Intent-to-Treat Sample Number ^a	Number of Patients Completing Week ^b											
			1		2		3		4		5		6	
			Patients		Patients		Patients		Patients		Patients		Patients	
			N	%	N	%	N	%	N	%	N	%	N	%
Org 3770 5 mg	30	29	29	100	27	93	25	86	20	69	18	62	15	52
Org 3770 15 mg	30	30	30	100	23	77	23	77	22	73	19	63	12	40
Org 3770 30 mg	30	28	28	100	22	79	20	71	19	68	15	54	11	39
Org 3770 60 mg	30	30	30	100	22	73	16	53	14	47	11	37	7	23
Placebo	30	28	28	100	27	96	25	89	22	79	20	71	17	61

^a Patients who received assigned medication and had one or more efficacy assessments.

^b Includes patients having efficacy data within 3 days of the scheduled visit.

Demographic Characteristics

Appendix 7.2.3.3.2 presents the demographic characteristics of the patients enrolled. There were more females enrolled in general (61% to 71%), but there were no large differences in the groups with respect to mean age.

Baseline Severity of Illness

Appendix 7.2.3.3.3 presents the Baseline Severity of Illness. There was no statistically significant difference.

Dosing Information

Appendix 7.2.3.3.4 presents the Dosing Information for the study. As noted it was a fixed dose study.

Concomitant Medications

57% to 70% patients received concomitant medications, most commonly chloral hydrate and non-narcotic analgesics.

Efficacy Results

For this review, efficacy was analyzed for the HAM D-21 Item scale, the HAM D Item #1 (mood), the MADRS and the CGI. These results are presented in Appendices 7.2.3.3.5-10. For each of the four parameters, the observed case analysis is presented for each visit, and the analysis of the last observation carried forward for the same parameter is presented for endpoint.

Patients treated with 5 mg/day and 30 mg/day of Org 3770 had a statistically significantly greater reduction in their HAM-D 21 scores at week 1 than placebo. Patients treated with 15 mg/day and 30 mg/day of Org 3770 had a statistically significantly greater reduction in their CGI score at week 1 than placebo. There were no other statistically significant findings.

Conclusion

More patients completed in the placebo group (60%) than in each of the treatment arms of the drug (<50%). The dropout rates increased at the higher doses (77% in the 60 mg group). The major reasons for dropouts in the drug group were lack of efficacy in the 5 and 15 mg dose groups and adverse events in the 30 and 60 mg dose groups. For the completers in the 60 mg group there is a trend for greater mean decreases in the total scores of the efficacy variables than the placebo patients, but the sample size is too small for statistical significance.

Overall, drug-placebo comparisons were not statistically significant for any of the four fixed doses. It is not possible to draw any conclusions for dose-response relationships from this

fixed dose study.

It should be noted that the other completed fixed dose study (#85002), was similarly designed (same dose groups and group sizes) but not placebo controlled, and it failed as well in terms of attempting to draw any conclusions for dose-response relationships.

7.2.4 Study 003-020/3220, Duration (Aug. '86-April '90)

7.2.4.1 Investigators and Location

Eric C. Dessain, M.D. (Aug. '86-April '88) and Thomas M. Walshe, M.D. (April '88-April '90) from the Institute for Psychopharmacologic Research, Inc., Danvers, MA

7.2.4.2 Study Plan

Objective

The primary objective of this trial was to evaluate the safety and efficacy of mirtazapine, amitriptyline, and placebo in the treatment of outpatients with major depression.

Population

Inclusion Criteria:

- .HAM-D 17 score of 18 or greater at baseline;
- .HAM-D 21 score not reduced by 20% or more between screening and baseline following 1-week of washout period with placebo; and
- .Age 18 or greater.

Exclusion Criteria:

- .Clinically significant renal, hepatic, respiratory, cardiovascular, cerebrovascular disease, or clinically significant abnormal findings at the screening examination;
- .Narrow-angle glaucoma;
- .Clinically significant prostatic hypertrophy
- .Seizure disorders;
- .Known drug allergies or hypersensitivity reactions to TCAs or related compounds;
- .Known clinically significant abnormal ECG;
- .Known hyperthyroidism;
- .Nursing mothers, pregnant women, and females of childbearing age not practicing birth control;
- .Patients with any of the following psychiatric diagnoses: schizophrenia; primarily anxiety disorder; adjustment disorder; or bipolar disorder; and
- .Patients on other psychotropic drugs; alcohol or substance abuse

within the previous six months; treatment with either ECT, MAOIs, or other psychotropic drugs within 3 months, 14 days, and 7 days of baseline respectively; known active suicidal tendencies; and known cognitive deficiencies.

Planned Study Conduct/Dosing Plan

This study was a 6 week, randomized, double-blind, active- and placebo-controlled study. A total of 150 patients, fifty in each group were planned for random assignment to 42 days of treatment with either mirtazapine, amitriptyline, or placebo. Eligible patients underwent a 1-week placebo washout, and after excluding placebo responders the patients were randomized to one of the 3 treatment groups: mirtazapine (5 to 35 mg/day), amitriptyline (40 to 280 mg/day), or matching placebo, taken in a single daily dose at bedtime. Patients who did not complete at least 39 consecutive days of drug treatment were considered premature terminations. After successful completion of the study, eligible patients were subsequently enrolled in a long term extension study primarily for collection of safety data.

Each mirtazapine capsule contains 5 mg of active drug and each amitriptyline 40 mg. The first week the maximum prescribed dose was 2 capsules, the second week the maximum prescribed dose was 4 capsules, and beginning with day 14 dose titration was left to the discretion of the investigator up to a maximum prescribed dose of 7 capsules daily (35 mg mirtazapine, 280 mg amitriptyline). Concomitant medication that could interfere with the action of mirtazapine or any other psychotropic drug was not allowed and the only hypnotic permitted was chloral hydrate (500 mg/day, qhs). Medications were dispensed during the weekly visits and at that time medication containers and unused medications were returned as well.

Efficacy/Safety Assessments

The HAM-D 21, the MADRS, the SDS, and the CGI constituted the efficacy measures and were performed at every visit. A responder was defined as a patient whose HAM-D 17 and 21 scores decreased by at least 50% from baseline. Seven weekly visits were scheduled, where visit 1 was at baseline (day 0). Safety assessments included physical examinations, electrocardiograms, clinical laboratories, ophthalmologic examinations, and pregnancy tests. Three years post initiation of the study an amendment for frequent CBC monitoring was added.

Analysis Plan

As in study 003-002

7.2.4.3 Study Conduct/Outcome

Patient Disposition

A total of 172 patients were screened and 130 enrolled: 44 in the mirtazapine group, and 43 in each of amitriptyline and placebo groups. All randomized patients who received at least one dose of study medication were included in the safety analyses. The number and percentage of patients who completed the study are shown in Table 7.2.4.3.1. The number and percentage of patients who discontinued prematurely are shown in Table 7.2.4.3.2.

TABLE 7.2.4.3.1
U.S. STUDY 003-020
PATIENT COMPLETION RATES

Treatment Group	Total Patients Randomized	Intent-to-Treat Sample Number ^a	Number of Patients Completing Week ^b											
			1		2		3		4		5		6	
			Patients		Patients		Patients		Patients		Patients		Patients	
			N	%	N	%	N	%	N	%	N	%	N	%
Amitriptyline	43	40	38	95	38	95	32	80	32	80	26	65	25	63
Org 3770	44	41	39	95	36	88	33	80	28	68	25	61	23	56
Placebo	43	39	37	95	35	90	32	82	30	77	28	72	24	62

^a Patients who received assigned medication and had one or more efficacy assessments.

^b Includes patients having efficacy data within 3 days of the scheduled visit.

TABLE 7.2.4.3.2
U.S. STUDY 003-020
NUMBER AND PERCENT OF PATIENTS DISCONTINUING TREATMENT BY REASON AND WEEK

Reason for Termination	Week 1			Week 2			Week 3			Week 4			Week 5			Week 6		
	Org 3770	Plac	Ami	Org 3770	Plac	Ami	Org 3770	Plac	Ami	Org 3770	Plac	Ami	Org 3770	Plac	Ami	Org 3770	Plac	Ami
	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)
Lack of Efficacy								1/38 (2.6)					2/38 (5.3)	2/31 (6.5)				
Adverse Event	1/44 (2.3)		1/43 (2.3)	1/41 (2.4)	1/39 (2.6)	2/40 (5.0)		3/38 (7.9)	3/38 (7.9)		2/34 (5.9)	2/35 (5.7)	6/38 (15.8)	1/31 (3.2)	3/33 (9.1)	1/30 (3.3)	2/28 (7.1)	3/28 (10.7)
Lost-to-Follow-Up	2/44 (4.5)	2/43 (4.7)	2/43 (4.7)							2/40 (5.0)							1/28 (3.6)	
Patient Never Took Drug	2/43 (4.7)																	

Patients who "discontinue treatment" in an interval are those patients whose last efficacy visit occurred in the previous interval.

N(%) is based on intent-to-treat efficacy data set.

% is percentage of all patients in a treatment group who did not discontinue in an earlier interval.

Demographic Characteristics

Appendix 7.2.4.3.1 presents the demographic characteristics of the patients enrolled. There were no statistically significant differences among the three treatment groups with respect to age, height, sex, or race. The overwhelming majority were Caucasian.

Baseline Illness Severity

Appendix 7.2.4.3.2 presents the Baseline Severity of Illness. There was no statistically significant difference.

Dosing Information

Appendix 7.2.4.3.3 presents the Dosing Information for the study. The mean mirtazapine dose at week 1 was 6.4 mg/day then successively increased to 23.5 mg/day at week 6.

Concomitant Medications

The most frequently taken concomitant medications were pain killers (NSAIDs and tylenol). Four patients in each of the treatment groups took chloral hydrate 500 mg/day, qhs. One patient took fiorinol (butalbital) for two days at the initiation of the study.

Efficacy Results

For this review, efficacy was analyzed for the HAM D-21 Item scale, the HAM D Item #1 (mood), the MADRS and the CGI. These results are presented in Appendices 7.2.4.3.4-8. For each of the four parameters, the observed case analysis is presented for each visit and the analysis of the last observation carried forward for the same parameter is presented for endpoint.

Org 3770 and the active control were statistically significantly more effective than placebo in relieving the symptoms of depression as measured by the HAM D-21 and the CGI at most timepoints for weeks 3 - 6. The LOCF confirms the observed cases results at all timepoints (only endpoint LOCF shown in the tables).

Conclusions

This study is a positive study. Org 3770 was statistically significantly more effective than placebo in relieving the symptoms of depression when evaluating the above mentioned parameters.

7.2.5 Study 003-021/3220, Duration (June '86-Sept. '88)

7.2.5.1 Investigators and Location

Roberto A. Dominguez, M.D. and Burton J. Goldstein, M.D.
University of Miami Medical School, Dept. of Psychiatry
Outpatient Clinic, Miami, FL.

7.2.5.2 Study Plan

Objective

The primary objective of this trial was to evaluate the safety and efficacy of mirtazapine, amitriptyline and placebo in the treatment of outpatients with major depression.

Population

As in study 003-020

Planned Study Conduct/Dosing Plan

As in study 003-020

Efficacy/Safety Assessments

As in study 003-020

Analysis Plan

As in study 003-002

7.2.5.3 Study Conduct/Outcome

Patient Disposition

The number and percentage of patients who completed the study are shown in Table 7.2.5.3.1. The number and percentage of patients who discontinued prematurely are shown in Table 7.2.5.3.2.

TABLE 7.2.5.3.1
U.S. STUDY 003-021
PATIENT COMPLETION RATES

Treatment Group	Total Patients Randomized	Intent-to-Treat Sample Number ^a	Number of Patients Completing Week ^b											
			1		2		3		4		5		6	
			Patients		Patients		Patients		Patients		Patients		Patients	
			N	%	N	%	N	%	N	%	N	%	N	%
Amitriptyline	50	48	46	96	41	85	35	73	37	77	31	65	27	56
Org 3770	50	45	43	96	41	91	39	87	39	87	26	58	22	49
Placebo	50	48	48	100	42	88	36	75	32	67	23	48	21	44

^a Patients who received assigned medication and had one or more efficacy assessments.

^b Includes patients having efficacy data within 3 days of the scheduled visit.

TABLE 7.2.5.3.2
U.S. STUDY 003-021
NUMBER AND PERCENT OF PATIENTS DISCONTINUING TREATMENT BY REASON AND WEEK

Reason for Termination	Week 1			Week 2			Week 3			Week 4			Week 5			Week 6		
	Org 3770	Plac	Ami	Org 3770	Plac	Ami	Org 3770	Plac	Ami	Org 3770	Plac	Ami	Org 3770	Plac	Ami	Org 3770	Plac	Ami
	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)
Lack of Efficacy													10/41 (24.4)	11/37 (29.7)		3/30 (10.0)	3/25 (12.0)	
Adverse Event	4/50 (8.0)	2/50 (4.0)		1/45 (2.2)	3/48 (6.3)	3/48 (6.3)	2/43 (4.6)	4/44 (9.3)	4/44 (9.3)		1/38 (2.6)	1/39 (2.6)	1/41 (2.4)	1/37 (2.7)	2/38 (5.3)	1/30 (3.3)		2/36 (5.6)
Lost-to-Follow-Up	1/50 (2.0)		2/50 (4.0)	1/45 (2.2)	1/48 (2.1)	1/48 (2.1)		2/44 (4.5)	1/44 (2.3)									2/36 (5.6)

Patients who "discontinue treatment" in an interval are those patients whose last efficacy visit occurred in the previous interval.

N(%) is based on intent-to-treat efficacy data set.

% is percentage of all patients in a treatment group who did not discontinue in an earlier interval.

Demographic Characteristics

Appendix 7.2.5.3.1 presents the demographic characteristics of the patients enrolled. There were no statistically significant differences between the three treatment groups with respect to age, height, sex, or race. The overwhelming majority were Caucasian.

Baseline Severity of Illness

Appendix 7.2.5.3.2 presents the Baseline Severity of Illness. There were no statistically significant differences between the three treatment groups.

Dosing Information

Appendix 7.2.5.3.3 presents the Dosing Information for the study. The mean dose at week 1 was 7.6 mg/day, then successively increased to 20.5 mg/day at week 6.

Concomitant Medications

The most frequently taken concomitant medications were pain killers (NSAIDs and tylenol). No patient took chloral hydrate.

Efficacy Results

For this review, efficacy was analyzed for the HAM D-21 Item scale, the HAM D Item #1 (mood), the MADRS and the CGI. These results are presented in Appendices 7.2.5.3.4-8. For each of the four parameters, the observed case analysis is presented for each visit, and the analysis of the last observation carried forward for the same parameter is presented for endpoint.

The results of the efficacy analysis of this study do not demonstrate that treatment with mirtazapine results in significant improvement in the treatment of major depressive illness as assessed by standardized methods. At some visits, efficacy parameters indicated significant improvement in depression in the mirtazapine group compared to placebo, but these results were not consistent. The active control group had better and more consistent results. The dropout rate for lack of efficacy in the mirtazapine and placebo groups were considerably high, while there were no such dropouts for the active control.

Conclusions

The results of the efficacy analysis of this study do not demonstrate that treatment with mirtazapine results in significant improvement in the treatment of major depressive illness as assessed by standardized methods. This can be considered a negative study, since efficacy for the active control was shown.

7.2.6 Study 003-022/3220, Duration (Sept. '86 - March '89)

7.2.6.1 Investigators and Location

James D. Bremner, M.D.; Bremner Research Institute, Olympia, WA.

7.2.6.2 Study Plan

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Objective

The primary objective of this trial was to evaluate the safety and efficacy of mirtazapine, amitriptyline and placebo in the treatment of outpatients with major depression.

Population

As in study 003-020

Planned Study Conduct/Dosing Plan

As in study 003-020

Efficacy/Safety Assessments

As in study 003-020

Analysis Plan

As in study 003-002

7.2.6.3 Study Conduct/Outcome

Patient Disposition

The number and percentage of patients who completed the study are shown in Table 7.2.6.3.1. The number and percentage of patients who discontinued prematurely are shown in Table 7.2.6.3.2.

TABLE 7.2.6.3.1
U.S. STUDY 003-022
PATIENT COMPLETION RATES

Treatment Group	Total Patients Randomized	Intent-to-Treat Sample Number ^a	Number of Patients Completing Week ^b											
			1		2		3		4		5		6	
			Patients		Patients		Patients		Patients		Patients		Patients	
			N	%	N	%	N	%	N	%	N	%	N	%
Amitriptyline	50	50	50	100	47	94	45	90	43	86	40	80	40	80
Org 3770	50	49	49	100	47	96	46	94	44	90	42	86	37	76
Placebo	50	50	50	100	48	96	46	92	45	90	42	84	36	72

^a Patients who received assigned medication and had one or more efficacy assessments.

^b Includes patients having efficacy data within 3 days of the scheduled visit.

TABLE 7.2.6.3.2
U.S. STUDY 003-022
NUMBER AND PERCENT OF PATIENTS DISCONTINUING TREATMENT BY
REASON AND WEEK

Reason for Termination	Week 1			Week 2			Week 3			Week 4			Week 5			Week 6		
	Org 3770	Plac	Ami	Org 3770	Plac	Ami	Org 3770	Plac	Ami	Org 3770	Plac	Ami	Org 3770	Plac	Ami	Org 3770	Plac	Ami
	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)
Lack of Efficacy											1/47 (2.1)		2/47 (4.3)	3/46 (6.5)	3/45 (6.7)	1/43 (2.3)	3/42 (7.1)	
Adverse Event	1/50 (2.0)			2/49 (4.1)	1/50 (2.0)	3/50 (6.0)		1/48 (2.1)	1/47 (2.1)			1/46 (2.2)	2/47 (4.2)	1/46 (2.2)	1/45 (2.2)		1/42 (2.4)	1/41 (2.4)
Patient Improvement					1/50 (2.0)													
Lost-to-Follow-Up																1/43 (2.3)		

Patients who "discontinue treatment" in an interval are those patients whose last efficacy visit occurred in the previous interval.

N(%) is based on intent-to-treat efficacy data set.

% is percentage of all patients in a treatment group who did not discontinue in an earlier interval.

Demographic Characteristics

Appendix 7.2.6.3.1 presents the demographic characteristics of the patients enrolled. There were no statistically significant differences among the three treatment groups with respect to age, height, sex, or race. The overwhelming majority were Caucasian and the majority in each group were female.

Baseline Severity of Illness

Appendix 7.2.6.3.2 presents the Baseline Severity of Illness. There were no statistically significant differences among the three treatment groups with respect to prior psychotropic therapy, current treatment status, or current disease condition.

Dosing Information

Appendix 7.2.6.3.3 presents the Dosing Information for the study. The mean mirtazapine dose at week 1 was 9.6 mg/day, successively increased to 30.8 mg/day at week 6.

Concomitant Medications

The most frequently taken concomitant medications were pain killers (NSAIDs and tylenol). Seven patients in the Org 3770 and amitriptyline groups and 10 in the placebo group took chloral hydrate.

Efficacy Results

For this review, efficacy was analyzed for the HAM D-21 Item scale, the HAM D Item #1 (mood), the MADRS and the CGI. These results are presented in Appendices 7.2.6.3.4-8. For each of the four parameters, the observed case analysis is presented for each visit, and the analysis of the last observation carried forward for the same parameter is presented for endpoint.

Both Org 3770 and amitriptyline were statistically significantly more effective than placebo in relieving the symptoms of depression as measured by the HAM D-21. Org 3770 was also statistically significantly more effective than placebo in relieving mood disturbance as measured by the HAM D Item #1. The positive results for both Org 3770 and amitriptyline were somewhat less consistent on the other efficacy measures, but both active drugs were statistically significantly more effective than placebo in relieving the symptoms of depression at endpoint.

Conclusions

This study was somewhat different than the others in that the enrolled patients had considerably higher scores in their baseline values, a higher percentage required the maximum dose, the mean dosing was higher and a higher percentage were completers than in other studies. Org 3770 was statistically significantly more effective than placebo in relieving the symptoms of depression when evaluating the above mentioned parameters.

7.2.7 Study 003-023 Duration (Jan. '87 - Feb. '90)

7.2.7.1 Investigator and Location

James Halikas, M.D. University of Minnesota Medical School
Minneapolis, Minnesota

7.2.7.2 Study Plan

Objective

The primary objective of this trial was to evaluate the safety and efficacy of Org 3770, trazodone, and placebo in the treatment of older adult (i.e., $\geq$ 55 years of age) outpatients with major depression.

Population

As in study 003-020, except for age criteria.

Planned Study Conduct/Dosing Plan

As in study 003-020. Maximum trazodone dose was set at 280 mg/day.

Efficacy/Safety Assessments

As in study 003-020, except the protocol was amended to include weekly assessments of WBC with differentials.

Analysis Plan

As in study 003-002

7.2.7.3 Study Conduct/Outcome

Patient Disposition

The number and percentage of patients who completed the study are shown in Table 7.2.7.3.1. The number and percentage of patients who discontinued prematurely are shown in Table 7.2.7.3.2.

TABLE 7.2.7.3.1
U.S. STUDY 003-023
PATIENT COMPLETION RATES

Treatment Group	Total Patients Randomized	Intent-to-Treat Sample Number ^a	Number of Patients Completing ^b Week											
			1		2		3		4		5		6	
			Patients		Patients		Patients		Patients		Patients		Patients	
			N	%	N	%	N	%	N	%	N	%	N	%
Org 3770	50	49	49	100	49	100	43	88	42	86	39	80	37	76
Placebo	50	49	48	98	45	92	41	84	40	82	37	76	34	69
Trazodone	50	48	48	100	44	92	40	83	38	79	34	71	32	67

^a Patients who received assigned medication and had one or more efficacy assessments.

^b Includes patients having efficacy data within 3 days of the scheduled visit.

TABLE 7.2.7.3.2
U.S. STUDY 003-023
NUMBER AND PERCENT OF PATIENTS DISCONTINUING TREATMENT BY
REASON AND WEEK

Reason for Termination	Week 1			Week 2			Week 3			Week 4			Week 5			Week 6		
	Org 3770	Plac	Traz	Org 3770	Plac	Traz	Org 3770	Plac	Traz	Org 3770	Plac	Traz	Org 3770	Plac	Traz	Org 3770	Plac	Traz
	(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)
Lack of Efficacy					1/49 (2.0)			3/47 (6.4)	2/45 (4.4)	1/46 (2.2)	1/42 (2.4)							
Adverse Event	1/50 (2.0)	1/50 (2.0)	1/50 (2.0)		1/49 (2.0)	3/48 (6.3)	3/49 (6.1)	1/47 (2.1)	1/45 (2.2)	1/46 (2.2)	1/42 (2.4)	4/42 (9.6)	2/42 (4.8)	3/40 (7.5)	3/38 (7.9)			
Lost-to-Follow-Up								1/47 (2.1)		2/46 (4.3)								
Patient Never Took Drug			1/50 (2.0)															

Patients who "discontinue treatment" in an interval are those patients whose last efficacy visit occurred in the previous interval.

N(%) is based on intent-to-treat efficacy data set.

% is percentage of all patients in a treatment group who did not discontinue in an earlier interval.

Demographic Characteristics

Appendix 7.2.7.3.1 presents the demographic characteristics of the patients enrolled. There were no statistically significant differences among the three treatment groups with respect to age, sex, or race. The overwhelming majority were Caucasian, and 43% of the mirtazapine arm (59% for placebo and 60% for Trazodone) were female.

Baseline Severity of Illness

Appendix 7.2.7.3.2 presents the Baseline Severity of Illness. There were no statistically significant differences among the three treatment groups.

Dosing Information

Appendix 7.2.7.3.3 presents the Dosing Information for the study. The mean mirtazapine dose at week 1 was 10.0 mg/day, then successively increased to 28.7 mg/day at week 6.

Concomitant Medications

The most frequently taken concomitant medications were pain killers (NSAIDs and tylenol). No patients took chloral hydrate.

Efficacy Results

For this review, efficacy was analyzed for the HAM D-21 Item scale, the HAM D Item #1 (mood), the MADRS and the CGI. These results are presented in Appendices 7.2.7.3.4-8. For each of the four parameters, the observed case analysis is presented for each visit, and the analysis of the last observation carried forward for the same parameter is presented for endpoint.

Org 3770 was statistically significantly more effective than placebo in relieving the symptoms of depression as measured by the HAM D-21 and MADRS, at week 2, week 4 and LOCF endpoint; the mood item #1 and CGI did not show mirtazapine to be superior to placebo. Trazodone was not statistically significantly more effective than placebo at endpoint in any variable.

Conclusions

The sponsor considers this study positive despite the equivocal results. I disagree with the sponsor's conclusion. Despite the high completion rates in this study (76% for Org 3770, 69% for placebo, and 67% for trazodone) and only one premature termination for lack of efficacy in the Org 3770 group, this can not be considered a study that clearly shows mirtazapine is superior to placebo in the treatment of depression. The low doses achieved in the trazodone arm (maximum allowed dose of 280 mg/day) of this study, is a possible reason for the active control not to show efficacy. Some studies have shown that trazodone doses of 300-400 mg/day are needed to achieve efficacy.

7.2.8 Study 003-024 Duration (Nov. '86 - July '88)

7.2.8.1 Investigator and Location

Ward T. Smith, M.D., Pacific Northwest Clinical Research Institute, Portland, Oregon

7.2.8.2 Study Plan

Objective

The primary objective of this trial was to evaluate the safety and efficacy of Org 3770, amitriptyline, and placebo in the treatment of outpatients with major depression.

Population

As in study 003-020

Planned Study Conduct/Dosing Plan

As in study 003-020

Efficacy/Safety Assessments

As in study 003-020.

Analysis Plan

As in study 003-002

7.2.8.3 Study Conduct/Outcome

Patient Disposition

The number and percentage of patients who completed the study are shown in Table 7.2.8.3.1. The number and percentage of patients who discontinued prematurely are shown in Table 7.2.8.3.2.

TABLE 7.2.8.3.1
U.S. STUDY 003-024
PATIENT COMPLETION RATES

Treatment Group	Total Patients Randomized	Intent-to-Treat Sample Number ^a	Number of Patients Completing Week ^b											
			1		2		3		4		5		6	
			Patients		Patients		Patients		Patients		Patients		Patients	
			N	%	N	%	N	%	N	%	N	%	N	%
Amitriptyline	50	49	48	98	48	98	45	92	44	90	39	80	35	71
Org 3770	50	50	49	98	48	96	46	92	45	90	36	72	30	60
Placebo	50	48	48	100	46	96	44	92	43	90	29	60	27	56

^a Patients who received assigned medication and had one or more efficacy assessments.

^b Includes patients having efficacy data within 3 days of the scheduled visit.

TABLE 7.2.8.3.2
U.S. STUDY 003-024
NUMBER AND PERCENT OF PATIENTS DISCONTINUING TREATMENT BY
REASON AND WEEK

Reason for Termination	Week 1			Week 2			Week 3			Week 4			Week 5			Week 6		
	Org 3770	Plac	Ami	Org 3770	Plac	Ami	Org 3770	Plac	Ami	Org 3770	Plac	Ami	Org 3770	Plac	Ami	Org 3770	Plac	Ami
	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)
Lack of Efficacy								1/46 (2.2)			1/44 (2.3)		3/45 (11.1)	13/43 (30.2)	1/45 (2.2)	2/36 (5.6)	1/29 (3.4)	
Adverse Event		1/50 (2.0)	1/50 (2.0)	2/50 (4.0)	1/48 (2.1)	1/49 (2.0)	1/48 (2.1)	1/46 (2.2)	2/48 (4.2)				4/45 (8.9)		4/45 (8.9)	1/36 (2.8)		3/39 (7.7)
Lost-to-Follow-Up		1/50 (2.0)			1/48 (2.1)		1/48 (2.1)			1/46 (2.2)		1/46 (2.2)		1/43 (2.3)		1/36 (2.8)		
Patient Completed															1/45 (2.2)		1/29 (3.4)	

Patients who "discontinue treatment" in an interval are those patients whose last efficacy visit occurred in the previous interval.

N(%) is based on intent-to-treat efficacy data set.

% is percentage of all patients in a treatment group who did not discontinue in an earlier interval.

Demographic Characteristics

Appendix 7.2.8.3.1 presents the demographic characteristics of the patients enrolled. There were no statistically significant differences among the three treatment groups with respect to age, sex, or race. The overwhelming majority were Caucasian and 54% of the mirtazapine arm (67% for placebo and 51% for amitriptyline) were female.

Baseline Severity of Illness

Appendix 7.2.8.3.2 presents the Baseline Severity of Illness. There were no statistically significant differences among the three treatment groups.

Dosing Information

Appendix 7.2.8.3.3 presents the Dosing Information for the study. The mean dose of mirtazapine at week 1 was 9.8 mg/day, successively increased to 22.0 mg/day at week 6.

Concomitant Medications

The most frequently taken concomitant medications were pain killers (NSAIDs and tylenol) and estrogen for menopausal symptoms. 4 placebo and one Org 3770 patients took chloral hydrate.

Efficacy Results

For this review, efficacy was analyzed for the HAM D-21 Item scale, the HAM D Item #1 (mood), the MADRS and the CGI. These results are presented in Appendices 7.2.8.3.4-8. For each of the four parameters, the observed case analysis is presented for each visit and the analysis of the last observation carried forward for the same parameter is presented for endpoint.

Org 3770 was statistically significantly more effective than placebo in relieving the symptoms of depression on all 4 measures of efficacy at some timepoints and for all four measures at LOCF endpoint. Amitriptyline was also superior to placebo on all four outcomes, often showing numerically greater improvement than Org 3770.

Conclusions

This study is one of the positive studies in the Org 3770 NDA. The active control effected the greatest decreases in the variables at endpoint, but Org 3770 was superior to placebo as well.

7.2.9 Study 84008 Duration (Nov. '84 - april '86)

7.2.9.1 Investigator and Location

The principle investigator was Prof. D. Petrovic of the Institute of Mental Health, Belgrade, Yugoslavia. The Co-investigators were Drs. Tomislav Sedmak, Stene Kolarovic, Irena Timotijevic, and Zoja Vuletic. The study was carried out from Nov '84-April '86.

7.2.9.2 Study Plan

Objective

The objective of this trial was to compare the safety and efficacy of the enantiomers of Org 3770 (4419 and 4420) and placebo in the treatment of depression.

Population

Inclusion Criteria:

- Score on the HAM D-21 of 21-50 on day 0.
- Ages for males between 18 and 65 years old and females 45-65 (unless there were effective birth control methods in use).
- Good physical health and no significant medical history and abnormal laboratory values.
- In-patients for four weeks.

Exclusion Criteria:

- A history of a primary diagnosis of
 - schizophrenia or other psychosis.
 - anxiety disorder
 - adjustment disorder
 - dysthymic or cyclothymic disorder
 - atypical depressive disorder.
 - known suicidal tendency.
- Heavy smokers (15 cigarettes or equivalent per day) or users of alcohol during the study.
- Treatment with ECT within 3 months of day 0.
- Patients on neuroleptics, MAO inhibitors, other anti-depressants, stimulants, appetite suppressors or other psychotropic drugs within seven days of day 0.
- Concomitant therapy with any CNS active drug, except for a night time sedative (1 gram of chloral hydrate for night-time sedation).

Planned Study Conduct/Dosing Plan

This was a five week, double-blind, placebo controlled study, with random allocation of 40 inpatients to each of the three treatment groups (Org 4419, Org 4420, or placebo). Patients were drug free for the 7 days prior to the initiation of the study.

Dose titration was permitted at the investigator's discretion in the first 3 weeks with the following guidelines: the maximum daily dose of the Org 4419 and 4420 was 20 mg in the first week; 40 mg at the end of the second week and a fixed dose of up to 60 mg for weeks 3 through 5. The dose was divided into morning and evening and orally administered.

Efficacy/Safety Assessments

The assessments of efficacy and the days on which they were done were as follows:

Neurotic/Endogenous Depression Rating Scale (NEDRS), Day 0; Montgomery-Asberg Depression Rating Scale (MADRS) Day 0, 7, 21, and 35; Brief Psychiatric Rating Scale (BPRS) Day 0, 7, 21, and 35; Global Assessment Scale (GAS) Day 0, 7, 14, 21, 28, and 35; Hamilton Psychiatric Rating Scale for Depression (HAM-D), Day 0 and 35.

Safety assessments and the days on which the assessments were done were as follows:

Laboratory (chemistry, hematology and urinalysis):
Screening, Days 14 and 35; PE and Vital Signs: Days 0, 7, 14, 21, 28, and 35.

Analysis Plan

The sponsor designated a set of efficacy parameters a priori for the analysis plan: GAS, BPRS, MADRS and HPDRS. An analysis of the covariance (one way classification with single regression) was to be applied to the scores (GAS) and factor scores (BPRS, MADRS and HPDRS) obtained for the efficacy measures at the end of treatment (5 weeks). The difference in treatment effect between the (+) enantiomer of Org 3770 and placebo and between the (-) enantiomer of Org 3770 and placebo was to be estimated with 95% confidence intervals. The Wilcoxon-rank-score test was to be used if the requirements for proper application of an analysis of covariance were not met.

To compare the potency of the enantiomers of Org 3770 a Student-test (or an appropriate non-parametric equivalent) was to be used to compare the mean daily dosages being given during the last 2 weeks of treatment.

The analysis plan in the protocol for this study was followed by the sponsor, but this division requested a different format: mean change analysis of the intent to treat group using both the observed case analysis and the last observation carried forward. The results presented in this synopsis present pair-wise comparisons (using the Wilcoxon Rank Sum Test and a one-way analysis of variance) of the active treatments against placebo.

7.2.9.3 Study Conduct/Outcome

Patient Disposition

The number and percentage of patients who completed the study are shown in Table 7.2.9.3.1. The number and percentage of patients who discontinued prematurely are shown in Table 7.2.7.3.2.

TABLE 7.2.9.3.1
NON-U.S. STUDY 84008
PATIENT COMPLETION RATES

Treatment Group	Total Patients Randomized	Intent-to-Treat Sample Number ^a	Number of Patients Completing Visit ^b									
			1		2		3		4		5	
			Patients		Patients		Patients		Patients		Patients	
			N	%	N	%	N	%	N	%	N	%
Org 4419	40	40	40	100	40	100	40	100	38	95	38	95
Org 4420	40	40	40	100	39	98	38	95	36	90	35	88
Placebo	41	41	41	100	40	98	40	98	39	95	39	95

^aPatients who received assigned medication and had one or more efficacy assessments.

^bVisit 1: Days 1 - 10

Visit 2: Days 11 - 17

Visit 3: Days 18 - 24

Visit 4: Days 25 - 31

Visit 5: Days 32 - 38

To be included in an interval, a patient must have remained in the study for the duration of that interval.

TABLE 7.2.7.3.2
NON-U.S. STUDY 84008
NUMBER AND PERCENT OF PATIENTS DISCONTINUING TREATMENT BY REASON AND VISIT

Reason for Termination	Visit 1			Visit 2			Visit 3			Visit 4			Visit 5		
	Org 4419	Org 4420	Plac	Org 4419	Org 4420	Plac	Org 4419	Org 4420	Plac	Org 4419	Org 4420	Plac	Org 4419	Org 4420	Plac
	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)
Inadequate Treatment Effect										2/40 (5.0)	1/38 (2.6)				
Adverse Reactions						1/41 (2.4)		1/39 (2.6)						1/36 (2.8)	
Refusal to Take Treatment/ Inadequate Compliance												1/40 (2.5)			
Reasons Not Related to Trial Treatment					1/40 (2.5)						1/38 (2.6)				

Patients who "discontinue treatment" in an interval are those patients whose last efficacy visit occurred in the previous interval.

N(%) is based on intent-to-treat efficacy data set.

% is percentage of all patients in a treatment group who did not discontinue in an earlier interval.

Demographic Characteristics

Appendix 7.2.9.3.1 presents the demographic characteristics of the patients enrolled. There were more females than males enrolled, especially in the Org 4420 arm (75% to 25%). There were no large differences in the groups with respect to mean age.

Baseline Severity of Illness

Appendix 7.2.9.3.2 presents the Baseline Severity of Illness. No tests of statistical significance were done for baseline scores, but the differences among the groups at baseline appear to be small.

Dosing Information

Appendix 7.2.9.3.3 presents the Dosing Information for the study. The mean doses for each of the enantiomers (4419 and 4420) at each interval were almost identical (approximately 20 mg, 25 mg, and 55 mg, for intervals 1, 2, and 3, respectively).

Concomitant Medications

All patients, except three from the Org 4419 group, received between 250 and 1000 mg chloral hydrate. Seven patients received a concomitant medication other than chloral hydrate. One of the patients took a benzodiazepine for 3 days during the study. Other concomitant medications included aspirin, methyldopa, ampicillin, and dipyridamole.

Efficacy Results

For this review, efficacy was analyzed for the HAM D-21 Item scale, the HAM D Item #1 (mood), the MADRS and the GAS. These results are presented in Appendices 7.2.9.3.4-7. For each of the four parameters, the observed case analysis and the last observation carried forward is presented.

There were no statistically significant differences between either of the enantiomers (Org 4419 and Org 4420) and placebo on any of the measures of efficacy at any point in time at which it was assessed during the course of treatment.

Conclusion

As mentioned in section 2.1, the (+) enantiomer blocks alpha₁ and the 5-HT₂ receptors, and the (-) enantiomer blocks the 5-HT₁ receptor. It is hypothesized that mirtazapine exerts its antidepressant effect via the inhibition of these two serotonin receptors. In this study, the enantiomers of Org 3770 (Org 4419 or Org 4420) individually were not more effective than placebo in

the treatment of depression when evaluating the above mentioned parameters.

7.2.10 Study 84023 Duration (June '84 - June '88)

7.2.10.1 Investigator and Location

The principle investigator was Dr. B. Alakare of Kirviranta, Finland. The study was carried out from Nov '84-April '86.

7.2.10.2 Study Plan

Objective

The objective of this trial was to compare the safety and efficacy of Org 3770 and placebo in the treatment of depression.

Population

Inclusion Criteria:

- Score on the HAM D-21 of 18 or more at day 0.
- Ages were between 18 and 75 years old.
- On the day of inclusion the duration of the present episode of the depression should have been at least two weeks and not exceed six months since diagnosis.
- If the depression is of a recurrent type, the patient should not have had more than 6 previous episodes which required hospitalization.

Exclusion Criteria:

- A history of a primary diagnosis of
 - schizophrenia or other psychosis.
 - anxiety disorder
 - adjustment disorder
 - dysthymic or cyclothymic disorder
 - atypical depressive disorder.
 - known suicidal tendency.
 - Drug or alcohol abuse.
- Heavy smokers (20 cigarettes or equivalent per day).
- Treatment with ECT within 3 months of day 0.
- Patients on neuroleptics, MAO inhibitors, other anti-depressants, stimulants, appetite suppressors or other psychotropic drugs within seven days of day 0.
- Concomitant therapy with any CNS active drug, except for a night time sedative (1 gram of chloral hydrate for night-time sedation).

Planned Study Conduct/Dosing Plan

This was a multicenter, six week, double-blind, placebo controlled study, with random allocation of 45 inpatients per group (Org 3770 or placebo). Preceding treatment, there was to be a placebo washout period from three to seven days. Patients were to be hospitalized for the first week of treatment.

The daily dose of Org 3770 was to be 15-50 mg in two divided doses. Dose titration was permitted at the investigator's discretion with increases allowed on days 15, 22 and 29. The optimized dose was to be fixed during days 29-42, unless clinically significant, side-effects emerged during treatment in which case the dose could be lowered one tablet at a time. The dose was divided into morning and evening and orally administered.

Dropouts were to be replaced when the reasons for dropout were unrelated to trial treatment.

Efficacy/Safety Assessments

The assessments of efficacy and the days on which they were done were as follows:

Montgomery-Asberg Depression Rating Scale (MADRS) Day 0, 14, 28, and 42; Brief Psychiatric Rating Scale (BPRS) Day 0, 14, 28, and 42; Global Assessment Scale (GAS) Day 0, 7, 14, 21, 28, 35 and 42; Hamilton Psychiatric Rating Scale for Depression (HAM-D), Day 0 and 42.

Safety assessments and the days on which the assessments were done were as follows:

Laboratory (chemistry, hematology and urinalysis): Screening, Days 21 and 42; PE and Vital Signs: Days 0, 14, 28, and 42; ECG: Day 0 and 42.

Analysis Plan

The analysis plan in the protocol for this study was followed by the sponsor, but this division requested a different format: mean change analysis of the intent to treat group using both the observed case analysis and the last observation carried forward. The results presented in this synopsis present pair-wise comparisons (using the Wilcoxon Rank Sum Test and a one-way analysis of variance) of the active treatments against placebo.

7.2.10.3 Study Conduct/Outcome

Patient Disposition

The number and percentage of patients who completed the study are

shown in Table 7.2.10.3.1. The number and percentage of patients who discontinued prematurely are shown in Table 7.2.10.3.2

TABLE 7.2.10.3.1
NON-U.S. STUDY 84023
PATIENT COMPLETION RATES

Treatment Group	Total Patients Randomized	Intent-to-Treat Sample Number ^a	Number of Patients Completing Visit ^b											
			1		2		3		4		5		6	
			Patients		Patients		Patients		Patients		Patients		Patients	
			N	%	N	%	N	%	N	%	N	%	N	%
Org 3770	59	59	58	98	52	88	46	78	40	68	37	63	37	63
Placebo	55	54	54	100	51	94	42	80	40	74	34	63	30	56

^aPatients who received assigned medication and had one or more efficacy assessments.

TABLE 7.2.10.3.2
NON-U.S. STUDY 84023
NUMBER AND PERCENT OF PATIENTS DISCONTINUING TREATMENT BY REASON AND INTERVAL

Reason for Termination	Visit 1		Visit 2		Visit 3		Visit 4		Visit 5		Visit 6	
	Org 3770	Plac	Org 3770	Plac	Org 3770	Plac	Org 3770	Plac	Org 3770	Plac	Org 3770	Plac
	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)
Inadequate Treatment Effect			2/59 (3.4)	1/54 (1.9)	5/53 (9.4)	7/51 (13.7)	4/46 (8.7)	3/43 (7.0)	1/40 (2.5)	3/40 (7.5)		2/34 (5.9)
Adverse Reactions							1/46 (2.2)					
Subject Well or Much Improved									1/40 (2.5)		1/38 (2.6)	
Refusal to Take Treatment/Inadequate Compliance		1/55 (1.8)	2/59 (3.4)	1/54 (1.9)	2/53 (3.8)	1/51 (2.0)		1/43 (2.3)				1/34 (2.9)
Reasons Not Related to Trial Treatment		1/55 (1.8)	1/59 (1.7)	1/54 (1.9)	1/53 (1.9)		1/46 (2.2)			3/40 (7.5)		
Suicide-no End of Trial Form Completed			2/59 (3.4)									

Patients who "discontinue treatment" in an interval are those patients whose last efficacy visit occurred in the previous interval.

N(%) is based on intent-to-treat efficacy data set.

% is percentage of all patients in a treatment group who did not discontinue in an earlier interval.

Visit 1: Days 1 - 10

Visit 2: Days 11 - 17

Visit 3: Days 18 - 24

Visit 4: Days 25 - 31

Visit 5: Days 32 - 38

Visit 6: Days 39 - 45

To be included in an interval, a patient must have remained in the study for the duration of that interval.

Demographic Characteristics

Appendix 7.2.10.3.1 presents the demographic characteristics of the patients enrolled. Females comprised 58% of the mirtazapine group and 48% of the placebo; the groups were similar with respect to mean age.

Baseline Severity of Illness

Appendix 7.2.10.3.2 presents the Baseline Severity of Illness. There were no statistically significant differences in the baseline scores.

Dosing Information

Appendix 7.2.10.3.3 presents the Dosing Information for the study. The mean dose for Org 3770 in the first week was 14.9 mg/day and in the last week 32.9 mg/day.

Concomitant Medications

The most commonly prescribed concomitant medications were chloral hydrate and benzodiazepines.

Efficacy Results

For this review, efficacy was analyzed for the HAM D-21 Item scale, the HAM D Item #1 (mood), the MADRS and the GAS. These results are presented in Appendices 7.2.10.3.4-7. For each of the four parameters, the weekly observed case analysis and the endpoint last observation carried forward is presented.

There were no statistically significant differences between Org 3770 and placebo on any of the measures of efficacy at any point in time.

Conclusion

This is the only study completely conducted in inpatients (weekend passes were given to some). The close supervision, however did not prevent the two suicides and the high number of dropouts and non-compliance due to lack of efficacy. In this study Org 3770 was not more effective than placebo in the treatment of depression, as measured by the above mentioned parameters.

7.2.11. Study 85027 Duration (April '86 - July '88)

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7.2.11.1 Investigator and Location

The principle investigator was Dr. M.C. Khan of Hartlepool, England.

7.2.11.2 Study Plan

Objective

The objective of this trial was to compare the safety and efficacy of Org 3770 and placebo in the treatment of depression.

Population

Inclusion Criteria:

- Ages for males and females between 18 and 65 years old.
- Rest same as in study 84023.

Exclusion Criteria:

- Rest same as in study 84023.

Planned Study Conduct/Dosing Plan

This was a multicenter, five week, double-blind, placebo controlled study, with random allocation of 50 per group (Org 3770 or placebo). Preceding treatment, there was to be a placebo washout period from three to seven days.

The daily dose of Org 3770 was to be 20-60 mg in two divided doses. Dose titration was permitted at the investigator's discretion. Week 1 the dose was 20 mg; Week 2 it was 20-30 mg; Week 3 it was 20-40 mg and Weeks 4 and 5 it was 20 to 60 mg. The dose was divided into morning and evening and orally administered.

Efficacy/Safety Assessments

The assessments of efficacy and the days on which they were done were as follows:

Montgomery-Asberg Depression Rating Scale (MADRS) Day 0, 14, 28, and 35; Brief Psychiatric Rating Scale (BPRS) Day 0, 14, 28, and 35; Global Assessment Scale (GAS) Day 0, 7, 14, 21, 28, and 35; Hamilton Psychiatric Rating Scale for Depression (HAM-D), Day 0, 14, 28, and 35.

Safety assessments and the days on which the assessments were done were as follows:

Laboratory (chemistry, hematology and urinalysis):
Screening, Days 14 and 35; Vital Signs: weekly; ECG: Day 0
and 35.

Analysis Plan

The analysis plan in the protocol for this study was followed by the sponsor, but this division requested a different format: mean change analysis of the intent to treat group using both the observed case analysis and the last observation carried forward. The results presented in this synopsis present pair-wise comparisons (using the Wilcoxon Rank Sum Test and a one-way analysis of variance) of the active treatments against placebo.

7.2.11.3 Study Conduct/Outcome

Patient Disposition

The number and percentage of patients who completed the study are shown in Table 7.2.11.3.1. The number and percentage of patients who discontinued prematurely are shown in Table 7.2.11.3.2

TABLE 7.2.11.3.1
NON-U.S. STUDY 85027
PATIENT COMPLETION RATES

Treatment Group	Total Patients Randomized	Intent-to-Treat Sample Number ^a	Number of Patients Completing Visit ^b									
			1		2		3		4		5	
			Patients		Patients		Patients		Patients		Patients	
			N	%	N	%	N	%	N	%	N	%
Org 3770	66	64	63	98	64	100	58	91	52	81	51	80
Placebo	66	66	66	100	59	89	55	83	55	83	48	73

^aPatients who received assigned medication and had one or more efficacy assessments.

TABLE 7.2.11.3.2
NON-U.S. STUDY 85027
NUMBER AND PERCENT OF PATIENTS DISCONTINUING TREATMENT BY
REASON AND INTERVAL

Reason for Termination	Visit 1		Visit 2		Visit 3		Visit 4		Visit 5	
	Org 3770	Plac	Org 3770	Plac	Org 3770	Plac	Org 3770	Plac	Org 3770	Plac
	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)
Inadequate Treatment Effect	1/66 (1.5)			1/66 (1.5)	2/64 (3.1)	4/61 (6.6)	2/58 (3.4)	1/57 (1.8)	1/55 (1.8)	2/55 (3.6)
Adverse Reactions					4/64 (6.3)		1/58 (1.7)			1/55 (1.8)
Subject Well or Much Improved				2/66 (3.0)					1/55 (1.8)	
Refusal to Take Treatment/Inadequate Compliance				2/66 (3.0)	1/64 (1.6)			1/57 (1.8)		1/55 (1.8)
Reasons Not Related to Trial Treatment	1/66 (1.5)			1/66 (1.5)					1/55 (1.8)	

Patients who "discontinue treatment" in an interval are those patients whose last efficacy visit occurred in the previous interval.

N(%) is based on intent-to-treat efficacy data set.

% is percentage of all patients in a treatment group who did not discontinue in an earlier interval.

Visit 1: Days 1 - 10

Visit 2: Days 11 - 17

Visit 3: Days 18 - 24

Visit 4: Days 25 - 31

Visit 5: Days 32 - 38

Demographic Characteristics

Appendix 7.2.11.3.1 presents the demographic characteristics of the patients enrolled. Females comprised 64% of the mirtazapine group and 70% of the placebo; the groups were similar with respect to mean age.

Baseline Severity of Illness

Appendix 7.2.11.3.2 presents the Baseline Severity of Illness. There were no statistically significant differences in the baseline scores.

Dosing Information

Appendix 7.2.11.3.3 presents the Dosing Information for the study. The mean dose of Org 3770 in the first week was 20.2 mg/day and in the last week 52.1 mg/day.

Concomitant Medications

Most commonly prescribed concomitant medications were chloral hydrate and benzodiazepines.

Efficacy Results

For this review, efficacy was analyzed for the HAM D-21 Item scale, the HAM D Item #1 (mood), the MADRS and the GAS. These results are presented in Appendices 7.2.11.3.4-7. For each of the four parameters, the observed case analysis and the last observation carried forward is presented.

There were statistically significant differences between Org 3770 and placebo at LOCF endpoint by Mood Item #1 and MADRS measures and weeks 3 and 4 for GAS but not at other efficacy time points.

Conclusion

This study had high completion rates, most dropouts were due to lack of efficacy and the baseline values suggest a less sick population compared to other studies. The statistical significance seen for Mood Item #1 and MADRS for some timepoints is supportive but not conclusive that Org 3770 was more effective than placebo in the treatment of depression.

7.2.4 Other Studies

The anxiolytic properties of mirtazapine were investigated in three studies (80036, 81011, and 80035). In these series of studies, a total of 150 patients received mirtazapine, 50 placebo, and 50 diazepam.

In study 80036, there was a significant difference between Org 3770 and placebo treatment in patients suffering from anxiety as measured by the Hamilton Anxiety Scale, Global Assessment Scale and Zung Anxiety Scale. There were no safety issues except for sedation.

In study 81011, there was reduction in psychic anxiety symptoms and no reports of adverse events.

In study 80035, diazepam and mirtazapine were comparable in their beneficial effect on sleep the night before an elective surgery. Org 3770 had also an anxiolytic effect. There were no safety issues except for more sedation "hangover" effect by Org 3770.

As mentioned in section 7.1, there were 9 short-term, double-blind, flexible-dose, non-US active control studies. In all of these studies, there was reduction in the mean HAM-D 21 item score in both treatment groups. There were no differences found between Org 3770 and the active controls, but without a placebo control these results are difficult to interpret.

7.3 Summary of Data Pertinent to Important Clinical Issues

7.3.1 Predictors of Response

The sponsor conducted meta-analyses to analyze responses in subpopulations. Efficacy and dose parameters of Org 3770 were compared in patients with age ≥ 65 and < 65 , female and male, and moderately and severely depressed patients. Statistical tests were conducted to evaluate the differences of the subpopulations when compared in terms of premature terminations rates, response rates, mean reduction in HAM-D score from baseline to endpoint and time of onset (time needed to reach 50% reduction in HAM-D) of antidepressant activity between Org 3770 and placebo. In the short-term US controlled studies, the differences noted in these groups were not statistically significant for the above mentioned parameters except for the mean doses prescribed. The ≥ 65 age group and females had statistically significantly higher mean doses prescribed than the younger group and in males. This is rather odd, since both women and the elderly have decreased clearance of mirtazapine and achieve higher AUCs for a given dose. An analysis of these topics is in Ms. Mele's Statistical Review.

7.3.2 Size of Treatment Effect

It is difficult to generalize about the treatment effect of Org 3770. When looking at the mean changes in the efficacy variables in the positive studies, Org 3770 appears to have an equivalent effect as the active control (amitriptyline). For example, in study # 003-020 the decrease in mean change from baseline in HAM-D 21 score for mirtazapine is 13.0 for the OC at week 6 and 10.3 for LOCF endpoint, for amitriptyline is 14.4 for the OC at week 6 and 11.5 for LOCF endpoint, and for placebo is 6.2 for the OC at week 6 and 4.8 for LOCF endpoint. Obviously, for the failed and the negative studies, the size of the treatment effect is comparable to placebo. Also, when comparisons are made across studies, the size of the treatment effect is not consistent, even though the dosages are similar.

7.3.3 Choice of Dose

The dose range in US studies was 3-60 mg/day and in Non-US studies it was 3-80 mg/day. The short-term, flexible-dose, US studies were performed in the same dose range (5-35 mg/day). The fixed dose studies had a maximum dose of 60 mg/day.

The two completed fixed dose studies did not show any statistically significantly different results between the doses selected. Aside from the fixed dose studies, the sponsor explored the dose-response relationship by pooling data and analyzing the mean reduction in HAM-D as a function of dose and the percentage

of responders at each dose at week 4. Although, a modal dose of 20 mg/day had the greatest mean reduction and the highest percentage of responders in the placebo-controlled studies, there was no supportive trend (the increase in percentage of responders and the mean reductions were not proportional to the dose).

In the labeling, the sponsor proposes a recommended initial dose of 15 mg/day and for patients not responding dose increases of up to a maximum of 45 mg/day. There is supportive but no firm evidence for the selected doses, particularly since the fixed dose studies failed.

7.3.4 Duration of Treatment

Organon did not perform any properly designed, randomized long term controlled trials to determine the efficacy of Org 3770 in the prevention and relapse of major depression.

7.4 Conclusions Regarding Efficacy Data

For this review, a positive response is considered a statistically significant difference between mirtazapine and placebo, a failed study is no statistical difference, and a negative study is no statistical difference between mirtazapine and placebo but statistically significant difference between active control and placebo. Of the 11 efficacy studies reviewed above, there are 4 positive studies (all in the 003 series #s 002, 020, 022 and 024), 1 negative study (# 003-021) and 6 failed studies (#s 003-003, 003-023, 84023, 85027, the fixed dose study 003-008 and the study of the enantiomers 84008). Overall, the studies not represented above, showed supportive evidence for the efficacy of mirtazapine, but are not part of the efficacy review due to their inappropriate designs.

On balance, the data from the studies described, provide support for the effectiveness of mirtazapine in the treatment of major depression, when it is administered in the recommended dose range of 15-45 mg/day.

8.0 Safety Findings

8.1 Methods

The mirtazapine NDA integrated safety summary was the main resource used to review the safety aspects of this drug. The integrated summary of safety includes data from all clinical pharmacology, efficacy and safety studies conducted worldwide. The number of subjects receiving any treatment worldwide is as follows:

Phase I (Clinical Pharmacology)

	Drug	Number of Patients
Single Dose	Mirtazapine	176
	Placebo	54
	Amitriptyline	12
	Diazepam	12
Multiple Dose	Mirtazapine	174
	Placebo	33

Phase II-III clinical trials: (for more detailed analysis please refer to Table 5.1.1)

Drug	# of Patients	Patient Years of Exposure*	
		N*	Pt. Yrs.
Mirtazapine	2796	2425	671.7
Placebo	605	494	71.4
Amitriptyline	666	615	158.5
All Active			
Controls**	1161	977	195.2

*The N for patient years of exposure is less than the actual number exposed, because no exposure data was available for the remainder.

**Amitriptyline was the primary active control used, others included: trazodone, clomipramine, diazepam, doxepin, and maprotiline.

Safety issues were evaluated on the basis of the dataset available: integrated safety summary; selected case report forms and narrative summaries; reports of deaths common and serious adverse effects; premature terminations from clinical trials; overdose reports; drug-drug interactions; and treatment emergent changes in vital signs, clinical laboratory values, and ECGs. Uncommon, serious adverse events were assessed using reports of deaths, premature terminations and serious adverse events (as defined below), while more common but less serious adverse reactions were identified through routinely collected safety

data. Deaths, suicides and treatment emergent adverse events are discussed section by section below.

8.2 Deaths

In the Org 3770 (mirtazapine) NDA, a total of 12 mirtazapine associated patient deaths are reported across all the clinical studies (US and foreign). These 12 deaths are summarized in Appendix 8.2. Three patients died in the mirtazapine arm of the US studies, 9 patients died in the mirtazapine arm of non-US studies (this number includes patient #18, from the ongoing study 86017 that has not been integrated into the database and is not included in the calculation of mortality rates). Additionally, 2 patients died in the non-US studies in the maprotiline arm.

There were no deaths in the placebo group. Among the 12 mirtazapine patients who died, nine were suicides, one was due to MI as a complication of asthma occurring 30 days after stopping the medication, another one was due to acute MI, and one was due to cholecystitis. The two deaths among the maprotiline patients were suicides.

In the opinion of this reviewer no causal relationship of the deaths to the study medication can be identified. As additional comments on four of the deaths: (i) Patient #403 from study 003-010 was a 61 year old male that had received mirtazapine for 24 weeks. He died of MI as a complication of asthma 30 days after stopping the medication. (ii) Patient #424 from study 003-010 was a 47 year old female that had received mirtazapine for 40 days (37.5 mg/day) and died of acute MI. Autopsy showed generalized arteriosclerosis with mild involvement of the coronaries. There was no evidence of orthostatic hypotension or ECG changes in the narrative summary or the CRF. (iii) Patient #112 from study 84023 was a 47 year old female that died of suicide due to overdose with amitriptyline, chlorprothixene, and mirtazapine (autopsy with toxic levels of amitriptyline and chlorprothixene, but not mirtazapine) after 13 days on study; (iv) Patient #111 from study 85004 was a 58 year old female who died of cholecystitis. The exact day of onset of symptoms is not clear, but on day 8 of treatment she was transferred to ICU, because of cholecystitis-induced shock. Her mirtazapine treatment was stopped on day 35 and she died anywhere from 2-10 days later (CRF and narrative summary unclear).

Overall mortality was determined for each treatment group using the integrated safety summary data base. For this purpose deaths were counted if the death occurred while in study and no more than 30 days after discontinuation of treatment. Tables 8.2.1 and 8.2.2 display the crude rate of mortality and the mortality adjusted for time of exposure to drug:

TABLE 8.1.1
MORTALITY: U.S. STUDIES

Drug	# of Patients	Patient Years of Exposure	Deaths	Crude Incidence	Mortality/100 Patient Years
Org 3770	1299	546.5	3	0.0023	0.55
Placebo	361	59.8	0	0	0
Active Controls ^a	301	104.2	0	0	0
Amitriptyline	252	99.6	0	0	0
Trazodone	49	4.6	0	0	0

TABLE 8.2.2
MORTALITY: NON-U.S. STUDIES

Drug	# of Patients	Patient Years of Exposure	Deaths	Crude Incidence	Mortality/100 Patient Years
Org 3770	1126	125.2	8	0.0071	6.38
Placebo	133	11.6	0	0	0
Active Controls ^a	676	91.0	2	0.0030	2.20
Amitriptyline	363	58.9	0	0	0
Trazodone	100	10.1	0	0	0
Clomipramine	58	6.0	0	0	0
Doxepin	80	7.8	0	0	0
Maprotiline	75	8.2	2	0.0267	24.39

^aThe numbers in this row are the sum of the numbers in the rows below (except the rates).

Assessment of the mortality rates comes from the 2425 patients for whom exposure data is available. The sponsor confirmed that the 11 deaths in the mirtazapine arm shown in the table all come from the 2425 patients with exposure data. The combined US and Non-US crude mortality incidence for mirtazapine is $11/2425 = 0.005$ with mortality rate/100 patient years being $11/671.7 \times 100 = 1.64$, while for the active controls $2/977 = 0.002$ and $2/195.2 \times 100 = 1.02$, respectively. The placebo arm had no deaths with an exposure of 71.4 patient years. As evident from the Deaths Reports suicides were the most common cause for deaths in the mirtazapine clinical trials. From these data it appears that both the crude mortality rates and the adjusted mortality rates are

higher in the mirtazapine arm as compared to placebo and active control. However, the differences are slight and unlikely to be meaningful.

8.3 Assessment of Dropouts

8.3.1 Overall Pattern of Dropouts

Tables 8.3.1.1 and 8.3.1.2 summarize the reasons for patients's premature termination in the database for phase 2 and 3 studies:

**TABLE 8.3.1.1
DISTRIBUTION OF ALL TREATED PATIENTS WHO
PREMATURELY TERMINATED* BY REASON AND TREATMENT GROUP
IN PHASE 2-3 U.S. STUDIES**

	ALL CONTROLLED				ALL CONTROLLED & UNCONTROLLED
TERMINATION REASON	ORG 3770 (N=580)	PLACEBO (N=361)	AMITRIPTYLINE (N=252)	TRAZODONE (N=49)	ORG 3770 (N=1299)
LACK OF EFFICACY	78 (13.4%)	77 (21.3%)	7 (2.8%)	2 (4.1%)	165 (12.7%)
ADVERSE REACTIONS	100 (17.2%)	27 (7.5%)	67 (26.6%)	9 (18.4%)	369 (28.4%)
PATIENT IMPROVED	11 (1.9%)	5 (1.4%)	4 (1.6%)	0	52 (4.0%)
LOST TO FOLLOW-UP	34 (5.9%)	24 (6.6%)	25 (9.9%)	0	98 (7.5%)
MISCELL- ANEOUS	55 (9.5%)	45 (12.5%)	19 (7.5%)	4 (8.2%)	146 (11.2%)
TOTAL DROPOUTS	278 (47.9%)	178 (49.3%)	122 (48.4%)	15 (30.6%)	830 (63.9%)

* Patients in the long-term extensions were counted as premature terminators if they did not complete the 20-week treatment period. If they discontinued treatment during one of the additional 24-week extensions, they were considered "Discontinuers," not premature terminators.

The number of dropouts in the US studies is high for all treatment groups. When considering only the controlled studies the three treatment groups of mirtazapine, placebo, and amitriptyline are similar with about a 50% dropout rate, but when all studies are taken into consideration, both controlled and uncontrolled, the mirtazapine dropout is approximately 64% (this probably reflects longer duration of treatment in the uncontrolled studies). The highest dropout rate in the placebo group is due to lack of efficacy (21.3%), while the highest rate of dropout is for adverse reactions in the amitriptyline group

(26.6%), and also in the mirtazapine group (17.2% in the controlled trials and 28.4% in all trials). Patient improvement accounted for very few dropouts. Controlled study discontinuations for lack of efficacy were considerably higher in the mirtazapine group compared to amitriptyline.

The next Table delineates dropouts in the foreign studies:

TABLE 8.3.1.2
DISTRIBUTION OF ALL TREATED PATIENTS WHO PREMATURELY TERMINATED
BY REASON AND TREATMENT GROUP IN PHASE 2-3 NON-U.S. STUDIES

	ORG 3770 (N=1053)	PLACEBO (N=133)	AMITRIPTYLINE (N=262)	ALL OTHER ACTIVE CONTROLS (N=349)
SUBJECT WELL OR MUCH IMPROVED	16 (1.5%)	2 (1.5%)	5 (1.9%)	11 (3.2%)
INADEQUATE TREATMENT EFFECT	89 (8.5%)	24 (18.0%)	18 (6.9%)	28 (8%)
ADVERSE REACTIONS	43 (4.1%)	1 (0.8%)	19 (7.3%)	20 (5.7%)
INADEQUATE COMPLIANCE	50 (4.7%)	10 (7.5%)	12 (4.6%)	14 (4.0%)
REASONS NOT RELATED TO TREATMENT	31 (2.9%)	8 (6.0%)	3 (1.1%)	14 (4.0%)
OTHER	1 (0.1%)	0	2 (0.8%)	0
TOTAL DROPOUTS	230 (21.8%)	45 (33.8%)	59 (22.5%)	87 (24.9%)

Note: N(%) are number and percentage of patients in a treatment group; patients may have had more than one reason for termination. Data were not available for Studies 22508, 80035, 80036, 80037, 81011, 81025, 81068, 81069, 82028, 82032, 84008, 85146, and the long-term extensions of Studies 85003 and 85146.

The total number of dropouts in the Non-US studies are considerably less than those in the US studies for all treatment groups - about 22% for the mirtazapine and amitriptyline treatment groups, and 34% for placebo. Lack of efficacy was the major reason in the placebo group (18%) and in the mirtazapine group (8.5%), while in the amitriptyline group it was the second highest (6.9%). The dropout rate due to adverse reactions in the amitriptyline group is 7.3%, and in the mirtazapine group is 4.1%. Patient improvement accounted for very few dropouts. The difference in the patterns of dropouts between the US and Non-US studies is notable; dropouts reported due to adverse reactions

are much less in the Non-US studies. In this reviewer's opinion, these patterns of reporting possibly could reflect different expectations of patients and investigators and cultural differences.

8.3.2 Adverse Events Associated With Dropouts

Appendix 8.3.2.1 outlines adverse experiences in short-term, placebo-controlled, U.S. studies for which $\geq 0.3\%$ of the Org 3770 treated patients were discontinued. The Non-US studies had a different reporting system (not as stringent as in the US), and also considerably fewer dropouts, hence are not included.

In the short-term, placebo-controlled, U.S. studies two adverse events (nausea and somnolence) lead to dropouts in $\geq 1\%$ of mirtazapine patients that also were ≥ 2 -fold of placebo. Table 8.3.2.1 presents the frequency of these adverse events:

Table 8.3.2.1

Adverse Experience (COSTART Term)	Org 3770 (N=453) N (%)	Placebo (N=361) N (%)
Somnolence	47 (10.4)	8 (2.2)
Nausea	7 (1.5)	0

8.4 Safety Findings With Other Specific Search Strategies

8.4.1 Search For Emergence of Suicidality

Tables 8.4.1.1 and 8.4.1.2 evaluate the suicide attempt and suicide rates from pooled data:

**TABLE 8.4.1.1
COMPLETED AND ATTEMPTED SUICIDES: ALL STUDIES***

Drug	Number of Patients	Patient Years of Exposure	Suicide Attempts	Suicide Attempts/ Number of Patients	Unadjusted Incidence/100 Patient Years
Org 3770	2425	671.7	29	0.012	4.32
Placebo	494	71.4	3	0.006	4.2
Active Controls	977	195.2	6	0.006	3.07

* Patient #23 in Study 82028 attempted suicide by jumping down the stairs. This patient is not included in the calculation of crude rates because exposure data is not available for this study.

**TABLE 8.4.1.2
COMPLETED SUICIDES: ALL STUDIES***

Drug	Number of Patients	Patient Years of Exposure	Suicides	Suicides/ Number of Patients	Unadjusted Incidence/100 Patient Years
Org 3770	2425	671.7	8	0.003	1.2
Placebo	494	71.4	0	0	0
Active Controls	977	195.2	2	0.002	1.02

* Patient #18 in Study 86017 (an ongoing study that has not been integrated into the database) committed suicide. This patient is not included in the calculation of mortality rates. The patient was taking Org 3770.

Appendix 8.4.1.1 includes four tables that delineate the rate of suicide attempts and rate of suicides in the US and Non-US studies separately. This is done to mark the significant variability in the rates of occurrence in US vs Non-US studies. In studies with exposure data, in the mirtazapine group 6 out of 1299 US patients and 23 out of 1126 Non-US patients attempted suicide, with 1 US and 7 Non-US completed suicides. There were no suicide attempts or completed suicides in the placebo or active controls of the US studies. In the Non-US studies there were 3 suicide attempts from placebo and 6 from active controls. There were no suicides from the placebo arm but 2 suicides from the active controls (both from the maprotiline treated group) of the Non-US studies. ("Suicide attempts" does not include ideation or completed suicides, but does include self inflicted injury and overdoses.)

When isolating the controlled studies only: there was one Org 3770 patient who attempted suicide in a US controlled study, while in the Non-US controlled studies there were 12 Org 3770 patients, 3 placebo patients, and 5 active control patients that

attempted suicide. There were no completed suicides in the US controlled studies; in the Non-US controlled studies there were 6 Org 3770 patients, 2 active control patients, and an additional Org 3770 in the ongoing study that committed suicide.

As with deaths, the rates seem higher in the mirtazapine group, especially in the suicide attempts column. Suicide is a known outcome in some patients with chronic depression especially with long term followup, hence to find a causal relationship to the study drug is not possible with the incidence rates obtained here, particularly when expressed in terms of patient years of exposure.

8.4.2 Search For Serious Events

The Code of Federal Regulations (CFR) defines serious adverse events as "...any experience that is fatal or life-threatening, is permanently disabling, requires inpatient hospitalization, or is a congenital anomaly, cancer, or overdose" (21 CFR § 312.32). The total phase 2-3 database incidence rate of serious adverse events was 3% in the mirtazapine group, 1.8% in the placebo, and 3.3% from active controls. 78 patients reported serious adverse experiences from the US studies and 87 patients from the Non-US studies. From the US studies, of the 78 total the mirtazapine group reported 56 patients with serious adverse experiences from the uncontrolled study 003-010 and 9 from various controlled studies. (The remaining 13 were reported in the placebo and active control groups). All serious adverse events are discussed under specific headings: deaths, suicides, cardiovascular, vital signs, laboratories, other important events considered potentially drug related or otherwise. Data sources were the integrated safety summary, patient narratives and case report forms.

8.5 Other Safety Findings

8.5.1 ADR Incidence Table And AE Lists

The spontaneous reports of adverse events were classified by body system using Coding Symbols for Thesaurus of Adverse Reaction Terms II (COSTART) in the US studies and Record of Symptoms Emerging (ROSE) in the Non-US studies. The Non-US studies had a different reporting system (not as stringent as in the US), and also considerably fewer adverse events and dropouts were reported, hence only the US studies are considered when preparing the tables and appendices.

8.5.1.1 The 1% Table

Appendix 8.5.1.1 includes all adverse events in the short-term, placebo-controlled, US studies (all in the 003 series #s 003-002, -003, -008, -020, -021, -022, -023, and -024) having an incidence

of $\geq 1\%$ in the mirtazapine group. This group of 8 studies were pooled and the rest left out because: (i) they are placebo-controlled studies; (ii) all 8 are similarly designed and conducted; (iii) individual study tables of adverse events are similar; (iv) the Non-US placebo-controlled studies, as mentioned above employed a different reporting system; and (v) the rest of studies were either not placebo-controlled or were open-label.

8.5.1.2 Dose Response For Common Adverse Events

There is one fixed-dose, placebo-controlled (003-008) and another fixed-dose, but not placebo-controlled study (85002) in this submission. It is not possible to draw any conclusion about dose response relationships due to the equivocal and non-significant results and the small sample size.

8.5.1.3 Common and Drug Related Adverse Events

From appendix 8.5.1.1 the following is a list of adverse events in short term US studies having an incidence of $\geq 5\%$ and reported at least twice as frequently as placebo:

Adverse Clinical Experience	Org 3770 (N=453)	Placebo (N=361)	Amitriptyline (N=193)	Trazodone (N=49)
Flu Syndrome	22 (4.9%)	9 (2.5%)	8 (4.1%)	5 (10.2%)
Increased Appetite	76 (16.8%)	7 (1.9%)	12 (6.2%)	3 (6.1%)
Weight Gain	54 (11.9%)	6 (1.7%)	13 (6.7%)	2 (4.1%)
Dizziness	33 (7.3%)	12 (3.3%)	27 (14.0%)	13 (26.5%)
Somnolence	243 (53.6%)	65 (18.0%)	115 (59.6%)	27 (55.1%)

8.5.1.4 Adverse Event Incidences on the Basis of Age and Gender

An analysis of adverse event incidences on the basis of age and gender was performed and submitted on 9/14/95 by the sponsor. The results are tabulated in appendix 8.5.1.4.1. The 13 adverse events analyzed come from appendix 8.5.1.1 and are adverse events

from the short-term US studies having an incidence of $\geq 1\%$ and reported at least twice as frequently as placebo. There were no statistically significant age differences and the only statistically significant gender difference was abnormal dreams, where it is reported in higher incidence among females.

8.5.1.5 Adverse Event Incidence Over Entire Phase 2-3 Integrated Primary Database

Appendix 8.5.1.5 includes all other adverse events reported from the clinical trials (US and Non-US) that are not reported in the incidence $\geq 1\%$ table (Appendix 8.5.1.1).

8.5.2 Laboratory Findings

8.5.2.1 Serum Chemistry

Appendix 8.5.2.1.1 lists the criteria and incidence of clinically significant chemistry laboratory abnormalities in the short-term US controlled studies (003-002, 003-003, 003-008, 003-020, 003-021, 003-022, 003-023, and 003-024). These include patients with at least one postbaseline laboratory assessment. Also listed is the Fisher's exact test (two-tailed), which shows statistical significance (at $p \leq 0.05$) for cholesterol and triglyceride elevations. It should be noted that these patients had normal baseline values and the changes were treatment emergent.

Appendix 8.5.2.1.2 tabulates the statistical summary of mean changes from baseline at week three, six and endpoint LOCF assessment for laboratory parameters of importance to this review. At $p \leq 0.05$ there is statistical significance (not accounting for multiple comparisons) in the increase of cholesterol, triglycerides, ALT, AST, LDH and Alkaline Phosphatase when comparing Org 3770 and placebo.

Areas of concern in this section are hepatotoxicity and fat metabolism, which will be considered separately:

Hepatic

In the integrated safety summary, the sponsor reports 14 patients treated with mirtazapine were prematurely terminated due to increases in one or more liver enzymes, and 8 patients experienced severe elevations. Only 2 patients overlapped, hence 20 patients treated with mirtazapine were prematurely terminated or experienced a serious event due to liver enzyme elevations.

My review of the integrated safety summary, appendices D.1-D.4 regarding the premature terminations and serious adverse events and patient narratives revealed higher numbers (given below) than reported by the sponsor. The discrepancy may lie in the categorization of the patients, since some patients had more than

one reason for premature termination or suffered more than one serious laboratory abnormality.

Based on my review, 20 (20/2796=0.72%) patients treated with mirtazapine were prematurely terminated due to increases in one or more liver enzymes, including GGT, alkaline phosphatase, LDH, ALT (SGPT), and AST (SGOT). There was only one (1/1161=0.09%) in the active control group and 2 (2/605=0.33%) in the placebo group that prematurely terminated for chemistry abnormalities, all due to increases in liver enzymes. It is interesting to note that all 20 Org 3770 premature terminations occurred in US studies.

9 patients (0.32%) treated with mirtazapine had serious adverse experiences involving elevation of one or more liver enzymes. There was 1 (0.17%) case (one of the 2 premature terminations) in the placebo and 2 (0.17%) (the one premature termination and an additional case) in the active control group of serious adverse experiences involving elevation of one or more liver enzymes. Here, 7 out of the 9 cases involving elevation of one or more liver enzymes occurred in US studies, and 2 in Non-US studies.

Not every serious adverse event is listed as a premature termination: according to the sponsors listings in appendix D.1-D.4 only 3 of the serious adverse events overlap with the premature termination's listings. Hence, overall 26 patients (26/2796=0.93%) treated with mirtazapine were prematurely terminated or experienced a serious event due to liver enzyme elevations, according to my review.

Individual cases of the serious adverse events and premature terminations were examined and are listed in appendix 8.5.2.1.3.

Based on my review, many of the cases listed in appendix 8.5.2.1.3, may be causally ascribed to mirtazapine. Several factors are considered in ascribing the causal relationship: (i) the discrepancy across treatments in incidence of serious adverse events and premature terminations due to adverse events; (ii) as shown in appendix 8.5.2.1.2, mean changes from baseline are statistically significant for ALT at 3 weeks (mean change of 8.92), 6 weeks (mean change of 4.22) and endpoint (mean change of 4.33), AST at 3 weeks (mean change of 4.33), LDH at endpoint (mean change of 4.26) and alkaline phosphatase at endpoint (mean change of 1.82); (iii) resolution of laboratory abnormalities after discontinuation of the drug; (iv) enzyme elevations recurring after rechallenge in two cases; (v) no other compounding factors or risks, such as a consistent pattern of concomitant medications (aside from alcohol) were discovered; and (vi) the severity of enzyme elevation in the mirtazapine group vs the placebo.

There is no evidence for any specific factors such as age and sex, or dose and duration of exposure that predisposes an

individual for liver enzyme elevation. When evaluating the mean changes from baseline, there is a hint of an effect on the liver such as enzyme elevation and other liver function test abnormalities (Albumin, Bilirubin, and total protein) during early exposure which then resolves with continued treatment (this is common with many drugs). As a risk factor for hepatotoxicity, concomitant ingestion of alcohol stood out, as illustrated by case #392. This case and the Drug-Drug Interaction study (reviewed in section 8.9) underscore the necessity of abstaining from alcohol while on this drug, since the patient received the drug for nine months without difficulty prior to the drinking episode.

Despite the apparent causal relationship, the liver enzyme elevations are modest and transient in the vast majority, return to normal with continued exposure and resolve completely without sequelae in the premature termination cases. There is agreement in the assessment of the above with both agency internal consultant Dr. John Senior and company consultant Dr. Paul Watkins. Although, Dr. Senior recommended a conservative approach with a liver enzyme monitoring protocol in place, Dr. Watkins and the PDAC did not see a clear benefit in this recommendation. My recommendation is avoidance of Remeron use in patients with liver disease and alcohol abuse.

Fat Metabolism

In addition to hepatotoxicity, fat metabolism is an issue of concern. Statistically significant increases in cholesterol and triglyceride levels with mirtazapine are seen in the short-term US studies (see appendix 8.5.2.1.2), with a mean increase in cholesterol of 5.8 mg/dl and in triglycerides of 21.5 mg/dl. These increases were greater than the mean increase with amitriptyline.

In one US uncontrolled study LDL and VLDL were analyzed (N=49) and there was an increase from baseline ≥ 40.8 mg/dl in 33% of individuals, but the LDL/HDL ratio did not show significant increase.

Thus, there is compelling evidence that mirtazapine has a tendency to elevate cholesterol and triglyceride levels, again with no particular relationship to time, dose, age or sex. Considering that mirtazapine also causes weight gain and increased appetite (to be discussed later) the elevation of cholesterol and triglyceride levels may be a secondary effect of overeating. (All levels done were non-fasting). In non-US studies many patients were inpatients and hence with tightly-controlled diets, probably leading to a lower percentage of patients with cholesterol, glucose, and triglycerides elevations. However, the combination of weight gain and cholesterol level elevation may increase the index of risk factors predisposing to cardiovascular

disease.

Other Chemistry Issues

The 3 cases of prostatic acid phosphatase elevations (#s 945 and 365 from study 003-010 are premature terminations and # 45 from study 84050 a serious adverse event), need special mention. During preclinical studies and subchronic toxicity testing, 13 out of 13 Beagle dogs treated with Org 3770 experienced significant decrease in prostatic weight, compared to one placebo treated dog. To evaluate this a follow-up dog study was done, which was not revealing. These three isolated cases are difficult to assess. In the clinical studies there were no effects on mean acid phosphatase levels.

In summary: The serious, but rare adverse event of hepatitis and the more common occurrence of hepatic liver enzyme, triglyceride and cholesterol elevations can be causally ascribed to mirtazapine.

8.5.2.2 Hematology

To set internationally accepted standard definitions of adverse drug reactions and criteria for assessment of causality, the Council for International Organizations of Medical Sciences (CIOMS) met in Paris, first in 1989 to designate drug-induced liver disorders, and in 1990 for drug-induced cytopenia. Their recommendations for drug-induced cytopenia were published in the International Journal of Clinical Pharmacology, Therapy and Toxicology, Vol. 29 No. 2-1991 (75-81). I will enumerate their definitions and base my review on these recommendations:

Leukopenia < $3.0 \times 10^9/l$

Neutropenia < $1.5 \times 10^9/l$ (segmented polymorphonuclear cells and bands)

Severe neutropenia < $0.5 \times 10^9/l$

Agranulocytosis is severe neutropenia in association with the sudden onset of signs and symptoms of bacterial infection (fever, malaise, oropharyngeal lesions, etc.)

Thrombocytopenia < $100 \times 10^9/l$

Pancytopenia is anemia (hemoglobin < 10 g/l), neutropenia and thrombocytopenia

Aplastic anemia is pancytopenia (or bicytopenia) with bone marrow biopsy showing histological evidence of decreased cellularity in the absence of infiltration or fibrosis.

Criteria for assessing the causal relationship of a drug to any of the abnormalities are multifactorial. I will only describe the assessment of time to onset (for initial treatment):

Neutropenia anytime during treatment is compatible

Thrombocytopenia < 1 month of exposure is suggestive > 1 month is

compatible

Pancytopenia < 4 days is incompatible > 4 days is compatible.

Appendix 8.5.2.2.1 lists the sponsor's criteria and incidence of clinically significant hematology laboratory abnormalities in the short-term US controlled studies (003-002, 003-003, 003-008, 003-020, 003-021, 003-022, and 003-024). These include patients with at least one postbaseline laboratory assessment. Also listed is the Fisher's exact test (two-tailed), which does not show statistical significance (at $p \leq 0.05$) for any of the tests listed.

Appendix 8.5.2.2.2 includes the statistical summary of mean changes from baseline at week three, six and endpoint LOCF assessment for hematologic laboratory parameters of importance to this review. At $p \leq 0.05$ there is statistical significance in the decrease of neutrophils and bands and increase in eosinophils when comparing Org 3770 and placebo.

Overall, 15 patients ($15/2796=0.54\%$) treated with mirtazapine were prematurely terminated due to hematology reported adverse events: 11 ($11/2796=0.39\%$) were due to leukopenia and/or neutropenia. There were 2 patients $2/605=0.31\%$ (leukopenias) in the placebo group and 2 (leukopenias) ($2/1161=0.17\%$) in the active control group who prematurely terminated due to hematology adverse events. (In addition there is one agranulocytosis case in the active control group in the ongoing European study, not part of this database, although the case is discussed below).

7 patients (0.25%) (4 with leukopenia, one agranulocytosis, one pancytopenia with agranulocytosis, and one thrombocytopenia) treated with mirtazapine had serious adverse experiences (please see definition of serious adverse events in section 8.4.2) involving hematologic abnormalities. There were 3 (0.26%) serious hematologic events in the active controls and none in the placebo group. (In addition, there was the aforementioned case of agranulocytosis in the imipramine group of the ongoing European study).

Not every serious adverse event involving leukopenia is included as a premature termination: according to the sponsor's listings in appendix D.1-D.4 only 5 of the serious adverse events overlap with the premature termination listings. Hence, overall 13 different patients ($13/2796=0.46\%$) treated with mirtazapine were prematurely terminated due to leukopenic adverse events and/or experienced a serious leukopenic adverse event.

Patient narrative or CRF reviews of the premature terminations and serious adverse events (listed in sponsor's submission Appendix D.1-D.4) disclosed 20 additional notable cases of chronically low, periodic fluctuations, or one time episodes of reported decreases in WBCs and or neutrophils. Following this

discovery, the sponsor was asked to perform a thorough analysis of the data and report all cases (US and Non-US, Phases I, II, and III) with absolute neutrophil counts (ANC) of 1500 or less. That search revealed one normal volunteer from Phase I with ANC 1001-1500. The results from Phases II and III are listed in table 8.5.2.2.1:

Table 8.5.2.2.1
Distribution of Patients with ANC $\leq$ 1500
Phase II-III Studies

ANC ($\times 10^3/\mu\text{L}$)	0-500(%)	501-1000	1001-1500
Org 3770 (n=2796)	3 (0.11%)	5 (0.18%)	43 (1.54%)
Placebo (n=605)	0	1 (0.17%)	2 (0.11%)
Active Control (n=1161)	0*	2 (0.17%)	8 (0.69%)

*Does not include the agranulocytosis case from imipramine (the ongoing European study).

Appendix 8.5.2.2.3 summarizes 33 of these cases in a tabular format. Cases of special interest are reported below, the remaining (as Appendix 8.5.2.2.3 reveals) were one time episodes of declines, periodic fluctuations, or baseline presentations of low WBC or neutrophil counts. Units utilized for the WBC are $10^3/\mu\text{L}$. It should be noted that, of the total cases mentioned in the table above 7 met the criteria of neutropenia at baseline only, 3 at baseline and postbaseline, 28 had postbaseline neutropenia that resolved without interruption of their therapy and 9 had neutropenia at last visit.

Agranulocytosis or Severe Neutropenia:

Patient #671, (Study 003-010) a 41-year-old Caucasian male, was prematurely terminated from the study on Day 60 due to acute agranulocytosis, while on 60 mg/day dose of Org 3770. His baseline WBC was 7.93 and ANC was 4.96. On Day 53 the WBC was decreased to 3.46 and the ANC to 2.05. On Day 60, the patient presented with fever (101.3°F), bilateral submandibular swelling, severe myalgia, and severe pharyngitis. Laboratories on Day 61 showed the following: WBC count = $3.0 \times 10^3/\mu\text{L}$; lymphocytes = $2.46 \times 10^3/\mu\text{L}$; basophils = $0.09 \times 10^3/\mu\text{L}$; eosinophils = $0.24 \times 10^3/\mu\text{L}$; monocytes = $0.21 \times 10^3/\mu\text{L}$; and neutrophils = 0. The patient was hospitalized and treated with antibiotics. Bands and granulocytes began appearing after three days of antibiotic therapy normalizing within 7 days, and the patient recovered completely. Seven weeks after discontinuing Org 3770, the

patient's hematology values continued to remain normal.

Patient #224, (Study 85146) a 59-year-old female with screening WBC of 4, hemoglobin of 11.2 and platelet count of 176K, developed fever and a morbilliform rash on day 9 of Org 3770 (20 mg bid) treatment. She was admitted to the hospital, with a leukocyte count of 3.1, hemoglobin of 11.3 and platelet count of 39K with precipitous drop in these counts following in few hours (leukocyte count of 1.5, hemoglobin of 9.8 and platelet count of 20K). The medication was stopped and the next day the patient's fever disappeared and the skin rash had improved considerably, but the pancytopenia (anemia, leukopenia, and agranulocytosis with absolute neutrophil count of 6) worsened. A bone marrow aspiration was performed revealing "medullary aplasia in particular with respect to the white cell lines with some atypical erythroblasts and megakaryocytes present." Over the next few days the condition of the patient deteriorated as respiratory depression and a neurological shock syndrome developed. The patient was intubated and antibiotic therapy was started. Over the next two weeks the pancytopenia resolved and the patient improved clinically, and after 17 days, the tracheal tube was removed. The patient recovered without permanent damage. The patient had a history of Sjogren's Syndrome and was status post partial thyroidectomy a year prior to the study.

Patient #168, (Study 85003), a 41-year-old Caucasian female, with no relevant past medical history was prematurely terminated from the study (day 14) due to acute decline of WBC and neutrophils and increase in lymphocytes on day 14, while on 30 mg/day of Org 3770. At baseline the WBC was 3.9, the neutrophil was 45% and the lymphocytes were 47%; while on day 14, 2.5, 16% (ANC 475), and 69%, respectively. There was gradual recovery, reaching normal counts (4.3, 39% and 48%).

Patient #46, (Ongoing Study 86017) a 62-year-old male, developed agranulocytosis (leukocyte count = $1.9 \times 10^9/L$, neutrophils = 0%) on Day 44 of imipramine 112.5 mg treatment. Study medication was discontinued, and treatment with nortriptyline 100 mg/day was initiated the following day. The leukocyte count steadily increased and had returned to within normal range seven days later ($5.1 \times 10^9/L$).

Leukopenia/neutropenia:

Patient #1010, (Study 003-010) a 37-year-old male, experienced intermittent (on days 21, 56, and 137) then persistent (from day 242 until termination day 433) clinically significant decreases of WBC and neutrophils. The lowest neutrophil count was 1.33 (on day 56), and 140 days after stopping the drug the count was 1.39.

Patient #1024, (Study 003-010) a 36-year-old male, developed (on day 15) clinically significant decreases of WBC (3.56) and

neutrophils (1.38). He was prematurely terminated (day 19) and values normalized 17 days later.

Patient #167, (Study 003-010) a 38-year-old female, experienced wide fluctuations of WBC (highest 6.06 and lowest 2.93) and neutrophils (highest 4.26 and lowest 0.93) occasionally with clinically significant decreases. Because of this, she was prematurely terminated (day 112).

Patient #837, (Study 003-010), a 40 year-old Caucasian male, was lost to followup at day 31 while taking Org 3770 30 mg/day. At day 15 the neutrophil count was 1.45 and at day 31 1.7, with no drop in WBC.

Patient #217, (Study 003-010) a 44-year-old Caucasian female, was prematurely terminated from the study (day 30) due to myalgia, cough and pharyngitis, while on 37.5 mg/day dose of Org 3770. On Day 29 the WBC and neutrophils were decreased (2.62 and 1.24, respectively). 40 days later the patient's hematologic profile showed recovery, though the WBC and neutrophils were still low.

Patient #248, (Study 003-010) a 35-year-old female, experienced fluctuations of WBC and neutrophils. She was prematurely terminated (day 41 while on 45 mg/day dose) for thrush. Patient was rechallenged after thrush resolved, but the thrush recurred, and the drug was discontinued permanently. The fluctuations of the WBC and neutrophils did not coincide with the thrush. At day 14 her WBC was 4.36 and the neutrophil was 1.84; on day 57 (7 days after second discontinuation) 4.18 and 1.55, and on day 71 3.5 and 1.72, respectively.

Patient #408, (Study 003-010) a 40-year-old female, experienced decreases of WBC and neutrophils on days 268, 367, and day of termination 547, while on 60, 45, and 60 mg doses, respectively.

Patient #416, (Study 003-010) a 45-year-old Caucasian male, was prematurely terminated from the study (day 29) due to myalgias and pharyngitis, while on 45 mg/day dose of Org 3770. On Day 26 the neutrophils were decreased significantly (0.86), with liver enzyme elevations. The hematologic abnormality resolved within 3 days of discontinuation of study medication.

Patient #420, (Study 003-010) a 53-year-old female, experienced decreases of WBC and neutrophils on days 8 and 131, and decrease in RBC on day 131 that lasted until termination (day 353).

Patient #664, (Study 003-010) a 53-year-old Caucasian female, was prematurely terminated from the study (day 97) due to gradual but steady decline of neutrophils from day 58 onward. There were decreases recorded on days 30 and 51 as well. The neutrophil count was 1920/mcL on day 30 and 790/mcL on day 85. There was gradual recovery, reaching normal counts on day 143.

Patient #61, (Study 003-020/25) a 32-year-old male, was prematurely terminated from the study (day 70 of the long term study) due to lack of efficacy. Patient was treated with amitriptyline for 44 days then switched to Org 3770. 17 days into Org 3770 (10 mg) treatment, the patient had a decline in WBC (2.7) and neutrophils (ANC = 999), with gradual recovery, while continuing treatment.

Patient #84, (Study 003-020/25) a 35-year-old male, was prematurely terminated from the study (day 72) due to improvement. Patient was treated with Org 3770 (10 mg) and 22 days into the Org 3770 treatment patient had a decline in neutrophils (ANC = 684), with increases in lymphocytes, with normalization within a week.

Patient #67, (Study 003-003), a 52-year-old Caucasian male, was prematurely terminated from the study (day 27) due to gradual but steady decline of neutrophils and increase in lymphocytes from day 21 onward, while on 35 mg/day of Org 3770. Her neutrophil count was 40% on day 21 and 30% on day 27. It recovered 2 days after discontinuation.

Patient #29, (Study 003-003), is described under the chemistry section. The patient was prematurely terminated on day 13, because of symptomatic hepatitis. On day 14 the WBC was at 2.5 with normal neutrophils. The WBC recovered by day 21.

Patient #669, (Study 003-010) a 58-year-old male, experienced intermittent (on days 12, and 84) then persistent (from day 84 until termination day 94) clinically significant decreases of WBC (normal neutrophil count). Hematology values on day 122 were still low.

Patient #719, (Study 003-010) a 43-year-old male, was prematurely terminated (day 36) due to gradually declining WBC levels from day 21 on. At baseline the WBC was 3.8, and 3.47 on day 35.

Patient #124, (Study 003-010) a 60-year-old female, had low WBC levels at baseline, remained chronically low while in the study with intermittent episodes of clinically significant decreases of WBC. She withdrew from the study on day 413.

Patient #173, (Study 85146), a 39-year-old Caucasian female, was prematurely terminated from the study (day 42) due to acute decline of platelets (73 from baseline of 273) on day 42, while on 30 mg/day of Org 3770. There was complete recovery.

Neutropenia cases in the active control group:

Patient #24, (Study 85042), a 41-year-old Caucasian female, was prematurely terminated from the study (day 15) due to acute decline of WBC, while on amitriptyline. There was gradual

recovery, reaching normal counts on day 22.

Patient #147, (Study 85042), a 28-year-old female was treated with amitriptyline and 15 days into the treatment patient had a decline in WBC (2.5) and neutrophils (ANC = 1000). On day 36 (last day of treatment and available data) the WBC was 2.7. There is no further information.

Patient #9, (Study 85031), a 58-year-old female was treated with trazodone. On day 42 (last day of treatment and available data) the WBC was 4.2 and ANC = 984. There is no further information.

Patient #137, (Study 85003), a 27-year-old Caucasian male, was prematurely terminated from the study (day 33) due to low WBC ($3.5/\text{cm}^3$), while on doxepine. There was gradual recovery.

Neutropenia cases in the placebo group:

Patient #29, (Study 003-008) a 28-year-old female, was prematurely terminated from the study (day 14) due to lack of efficacy and drop in WBC. Baseline WBC and neutrophil counts were low (ANC = 1540), after 7 days of treatment with placebo the patient had a decline in WBC and neutrophils (ANC = 957), with normalization within a week.

In addition, to more fully evaluate the possible hematologic effects of mirtazapine, it may be helpful to evaluate the mean changes over an extended period.

Mean changes are depicted in appendix 8.5.2.1.2. Additionally, table 8.5.2.2.2 displays these mean changes from Week 3 through Week 28.

TABLE 8.5.2.2.2
MEAN CHANGES FROM BASELINE FOR WHITE BLOOD CELLS:
ALL U.S. CONTROLLED STUDIES

Laboratory Parameter (Units)		Org 3770	Placebo	Amitriptyline
WBC COUNT (x 10³/μL)				
Baseline	N	580	361	252
	Mean	7.3	7.6	7.3
Week 3	N	480	304	210
	Mean (Mean Change)	7.1 (-0.2)	7.3 (-0.2)	7.1 (-0.2)
Week 8	N	411	237	183
	Mean (Mean Change)	7.0 (-0.2)	7.3 (-0.2)	7.0 (-0.2)
Week 12	N	163	57	101
	Mean (Mean Change)	6.9 (-0.5)	7.5 (0.0)	7.0 (-0.4)
Week 20	N	124	35	81
	Mean (Mean Change)	7.3 (-0.1)	7.5 (0.1)	7.1 (-0.2)
Week 28	N	80	25	61
	Mean (Mean Change)	7.3 (-0.2)	7.8 (0.4)	7.0 (-0.5)
EOSINOPHILS (x 10³/μL)				
Baseline	N	580	361	252
	Mean	2.1	2.2	2.5
Week 3	N	480	303	209
	Mean (Mean Change)	2.5 (0.3)	2.2 (-0.1)	3.0 (0.4)
Week 8	N	411	237	183
	Mean (Mean Change)	2.6 (0.5)	2.2 (-0.1)	2.9 (0.3)
Week 12	N	162	57	101
	Mean (Mean Change)	2.5 (0.2)	2.2 (-0.3)	2.8 (0.0)
Week 20	N	124	35	81
	Mean (Mean Change)	2.1 (-0.2)	2.8 (0.2)	2.8 (0.0)
Week 28	N	80	25	61
	Mean (Mean Change)	2.0 (-0.2)	2.7 (0.0)	2.8 (0.0)
NEUTROPHILS (x 10³/μL)				
Baseline	N	580	361	252
	Mean	60.3	60.8	60.1
Week 3	N	480	304	209
	Mean (Mean Change)	58.2 (-1.8)	60.4 (-0.4)	60.3 (0.5)
Week 8	N	411	237	183
	Mean (Mean Change)	58.8 (-1.5)	59.9 (-0.6)	60.2 (0.1)
Week 12	N	163	57	101
	Mean (Mean Change)	57.9 (-2.5)	60.4 (0.6)	58.9 (-1.5)
Week 20	N	124	35	81
	Mean (Mean Change)	58.3 (-2.2)	61.2 (2.0)	59.0 (-1.8)
Week 28	N	80	25	61
	Mean (Mean Change)	58.6 (-2.0)	60.1 (-0.4)	60.9 (-1.1)

N = Number of patients with evaluable data; Mean = Mean value.

Org 3770 may be implicated as a possible cause of the agranulocytoses reported above. The pattern of hematological changes in these patients may correspond with typical cases of drug-induced agranulocytosis. Even though a case was observed in the imipramine group, this drug has been one of the mainstays of depression therapy for decades and leukopenia and agranulocytosis are not among its common adverse events.

Considering the above, and the serious adverse events and the premature terminations, there seems to be a cause and effect relationship between administration of mirtazapine and decreases in WBC and neutrophils. Excluding the cases with fluctuations of WBC and neutrophil levels, almost all the other severe cases described may be causally ascribed to mirtazapine. Several factors are considered in ascribing the causal relationship: (i) the discrepancy in incidences of serious adverse events and premature terminations due to adverse events between mirtazapine and placebo; (ii) although the incidence differences shown in appendix 8.5.2.1.1 are not statistically significant, the mean decreases in neutrophils and bands (appendix 8.5.2.2.1) are statistically significant compared to placebo; (iii) resolution of laboratory abnormalities after discontinuation of the drug was common; and (iv) no other compounding factors or risks, such as consistent pattern of concomitant medications, were discovered.

There is no pattern suggesting specific risk factors such as age, sex, dose, or duration of exposure for this adverse event. Because many patients were dropped from their study due to leukopenia, it is difficult to assess the possible outcomes for those individuals if they had continued on the drug.

Although clinically significant increases in eosinophils were observed in 2% (12/546) of Org 3770 patients, a similar percentage of placebo patients experienced this abnormality and a higher percentage of amitriptyline patients (6%) had a clinically significant increase in eosinophils.

In summary: The serious adverse events of agranulocytosis, pancytopenia, and the more common occurrences of neutropenia and leukopenia can be causally ascribed to mirtazapine. The recovery period from the agranulocytosis was rapid. Mirtazapine is chemically related to mianserin and when first introduced was known as 6-azamianserin. Mianserin (to be discussed in section 8.6.3), is a drug well known for its hematologic adverse events (in particular leukopenia and agranulocytosis).

8.5.2.3 URINE ANALYSIS

Appendix 8.5.2.3.1 lists the criteria and incidence of clinically significant urine analysis abnormalities in the short-term US placebo and amitriptyline controlled studies (003-020, 003-021, 003-022, and 003-024). These include patients with at least one postbaseline laboratory assessment. Also listed is the Fisher's exact test (two-tailed), which does not show statistical significance (at $p \leq 0.05$) for any of the tests listed.

There were no reports of serious adverse experiences or

premature terminations due to abnormalities in urinalysis parameters. For this section no individual cases were reviewed. From the available data it is apparent that no particular urine analysis abnormality can be attributed to mirtazapine.

8.5.3 VITAL SIGNS AND WEIGHT

Appendix 8.5.3.1 lists the criteria and incidence of clinically significant Vital Signs and Weight abnormalities in the short-term US controlled studies. These include patients with at least one postbaseline assessment. Also listed is the Fisher's exact test (two-tailed), which shows statistical significance for weight gain, when comparing mirtazapine with placebo.

The statistical summary of mean changes from baseline at week three, six and endpoint assessment of the Vital Signs were not significant, but the Weight increases were statistically significant (weight gain is discussed below).

Overall, 7 patients ($7/2796=0.25\%$) treated with mirtazapine were prematurely terminated due to Vital Signs related (excluding Weight) adverse events. There were 8/1161 (0.69%) in the active control group and none in the placebo group that prematurely terminated for Vital Signs abnormalities, all due to increases or decreases in blood pressure.

One (0.04%) patient (#262, study 030-010) treated with mirtazapine had serious adverse experience involving Vital Signs (hospitalization for hypertension 4 days after premature termination). There were no cases in the placebo and there was 1 (0.09%) in the active control group of reported serious adverse experiences involving Vital Signs.

Individual cases of the serious adverse events and premature terminations that occurred were examined and no significant findings were discovered. 5 out of the seven total cases that terminated prematurely in the mirtazapine group were due to increase in blood pressure (mild elevations), 2 due to hypotension and 1 due to orthostatic hypotension. During phase I testing orthostatic hypotension was the most commonly reported adverse event.

Evaluation of mean changes and significant postbaseline shifts for vital signs disclosed no differences between the mirtazapine and the placebo groups.

Weight gain

As appendix 8.5.3.1 shows, there is statistical significance (at $p<0.05$) for clinically significant weight gain, when comparing mirtazapine with placebo. Weight gain is one of the most frequently reported adverse event. 107 ($107/2796=3.81\%$) patients treated with mirtazapine were prematurely terminated due to weight increase. There were 3 ($3/1161=0.26\%$) in the active control group and 1 ($1/361=0.28\%$) in the placebo group that prematurely terminated for weight increase. All dropouts (except one mirtazapine patient) came from US studies.

Overall 15% of US patients and 5% of Non-US patients reported weight gain as an adverse event. Despite this reporting and dropout discrepancy between US and Non-US studies, the mean weight gain in the two groups as comparable. Amitriptyline and maprotiline reported weight gain with comparable percentages to mirtazapine, while much smaller percentages reported weight gain in other active control groups and in the placebo group. In all US controlled studies, the mirtazapine group had a gradual increase in mean body weight of 8.2 lbs, (6.0 for amitriptyline).

A trend towards increase in non-fasting triglycerides and cholesterol was noted with the weight gain. The incidence rate of clinically significant weight gain (> 7% change from baseline) in all US and non-US controlled studies was approximately 16% (short-term US studies was 7.5%). In US Un-controlled studies the rate was 32.1%. With lengthening exposure to the drug, both the numbers reporting clinically significant weight gain and the amount of gain rise. Extreme weight gain (defined as $\geq 10\%$ of baseline in 2 consecutive visits) of US patients was approximately 9.0% for both mirtazapine and amitriptyline, while $\geq 15\%$ gain at 2 or more consecutive visits was 3.1% for mirtazapine and 0% for amitriptyline.

Table 8.5.3.1 summarizes the mean changes for weight reported in the short-term US studies:

TABLE 8.5.3.1
MEAN CHANGES FROM BASELINE FOR WEIGHT:
SHORT-TERM U.S. CONTROLLED STUDIES

Vital Sign Parameter (Units)		Org 3770	Placebo	Amitriptyline
Weight (lbs)				
Baseline	N	453	361	193
	Mean	164.5	166.5	166.5
Week 1	N	426	343	181
	Mean (Mean Change)	166.6 (1.5)	166.3 (0.1)	166.1 (0.7)
Week 2	N	389	315	173
	Mean (Mean Change)	166.5 (2.3)	166.9 (0.2)	168.7 (1.5)
Week 3	N	361	294	156
	Mean (Mean Change)	168.8 (3.0)	165.7 (0.4)	167.5 (1.7)
Week 4	N	340	276	153
	Mean (Mean Change)	168.9 (3.5)	166.8 (0.2)	169.9 (2.2)
Week 5	N	292	229	135
	Mean (Mean Change)	169.3 (4.3)	165.5 (0.2)	168.3 (2.6)
Week 6	N	247	203	129
	Mean (Mean Change)	171.1 (4.4)	165.9 (-0.1)	166.6 (3.0)

N = Number of patients with evaluable data; Mean = Mean value.

The weight increase, when comparing Org 3770 and placebo, is statistically significant (p value <0.05) at every visit and endpoint.

When evaluating vital signs and weight gain it is apparent that

weight gain is a common and significant adverse event with clear causal relationship to the study medication. The continued weight gain with continued exposure, and the triglyceride and cholesterol elevations in conjunction with the weight gain, may place an individual at a higher long-term risk for cardiovascular complications.

8.5.4 ECG Findings and Other Cardiovascular Events

Overall, 19 patients (19/2796=0.68%) treated with mirtazapine were prematurely terminated due to cardiovascular adverse events: 4 (4/2796=0.14%) were due to palpitation; 4 (4/2796=0.14%) were due to tachycardia; 7 (7/2796=0.25%) were due to abnormal ECG; 2 (2/2796=0.07%) were due to myocardial infarctions (MI); there was also one ruptured aneurysm and one pulmonary embolus (PE). There were 3 cardiovascular (3/605=0.50%) premature terminations in the placebo group and 22 (22/1161=1.90%) in the active control group.

18 patients (0.64%) (5 ECG changes, 3 MIs, 2 chest pains, 1 cardiac arrest, 1 exaggerated vaso-vagal response, 1 ruptured aneurysm, 1 syncope, 1 coronary artery bypass graft (CABG), 1 transient ischemic attack (TIA), 1 hypertension (HTN), and 1 PE) treated with mirtazapine had serious adverse experiences involving the cardiovascular system. There were 4 (0.34%) serious cardiovascular events in the active controls (PE, angina, tachycardia and serious hypotension) and none in the placebo group.

Not every serious adverse event is included as a premature termination under the cardiovascular reasons for termination: according to the sponsors listings in appendix D.1-D.4 only 8 of the serious adverse events overlap with the premature termination's listings. Hence, overall 29 different patients (29/2796=1.04%) treated with mirtazapine (1.90% for active control) were prematurely terminated due to cardiovascular adverse events and/or experienced a serious cardiovascular adverse event.

Individual cases of special interest from the serious adverse events and premature terminations in the phase 2-3 trials were examined and some listed in appendix 8.5.4.1.

In the clinical pharmacology studies performed to examine the safety, tolerance, PD and PK characteristics of mirtazapine common safety concerns included: recurrent episodes of orthostatic hypotension (17/350) and syncope (4/350).

ECG Findings

Appendix 8.5.4.2 lists the criteria and incidence of clinically significant ECG abnormalities in the short-term US controlled studies. These include patients with at least one postbaseline ECG assessment. Also listed is the Fisher's exact test (two-tailed), which does not show statistical significance (at $p \leq 0.05$) for any of the tests listed.

Appendix 8.5.4.3 includes the statistical summary of mean changes

from baseline of the ECG parameters. There is statistically significant change in increased heart rate and prolongation of QTc when comparing mirtazapine to placebo; however the difference seen when comparing the active control to mirtazapine or to placebo is far greater than that seen for the mirtazapine and placebo comparison.

The above analyses include seven of the eight U.S. short-term placebo-controlled studies, for which ECG data exists.

Org 3770 does not appear to induce significant heart rate, PR, QRS, or QTc interval abnormalities. But, with respect to mean changes, Org 3770 induced a statistically but not clinically significant increase in heart rate (3.38 bpm) and QTc interval (4.3 msec). The magnitude of the increase induced by Org 3770, for both heart rate and QTc is significantly less than the increase induced by amitriptyline (13.33 bpm for heart rate and 17 msec for QTc interval). Also, the incidence of rhythm disturbances or ST/T wave abnormalities at either Weeks 3-4 or 6-8 was not statistically different when comparing Org 3770 and placebo treatments.

In summary, when evaluating cardiovascular adverse events and ECG abnormalities it is not apparent that there is a clear causal relationship to the study medication. There are indications that mirtazapine may have an influence on the conduction pathway in certain patients, as evidenced by 2 cases of LBBB, but Org 3770 did not have a statistically significant effect on the PR or QRS interval when compared to placebo.

The frequent episodes of orthostatic hypotension and exaggerated vasovagal responses experienced in the Phase I studies can be directly linked to the study drug. The two cases described above (patients #006, study 88005 and #028 study 22503) are illustrative of this fact.

Based on the data reviewed, the effect of Org 3770 on the ECG was of statistical but not clinical significance compared to placebo, and it appears to have a more benign cardiovascular profile than the active controls. However, it is difficult to discuss Org 3770's potential cardiovascular adverse effects, considering its possible link to conduction abnormalities, orthostatic hypotension, and vasovagal effects. It may be that certain patients would be susceptible to such adverse drug reactions.

8.5.5 Chest X-Ray

No such diagnostic test was performed.

8.5.6 Ophthalmology

Overall 525 patients (176 Org 3770, 137 amitriptyline, 35 trazodone and 177 placebo) had two ophthalmological examinations (baseline and follow-up) in the short term US studies and 136 patients (51 Org 3770, 55 amitriptyline, and 30 placebo) in the long term studies. The sponsor's special analysis revealed no particular increase in ophthalmological abnormality in any of the

treatment groups, both in short-term and long-term US studies. The percent and type of abnormalities were not different between Org 3770, placebo and active control, and no particular abnormality was overrepresented.

8.5.7 Special Studies

The anxiolytic properties of mirtazapine were investigated in three studies (80036, 81011, and 80035). In these series of studies, a total of 150 patients received mirtazapine, 50 placebo, and 50 diazepam. There were no unique safety findings in this population.

8.5.8 Withdrawal Phenomenon/Abuse Potential

To evaluate withdrawal symptoms, the sponsor used the description of the withdrawal syndrome associated with TCAs as described by Frenkel et al in 1992: "the most common complaint is of a 'flu-like' syndrome: nausea, vomiting, diarrhea, abdominal cramps, malaise, cold sweats, chills, dizziness, and headaches." Investigators conducted follow-up interviews after premature terminations and/or completion of studies. Most US studies, but none of the Non-US studies had follow-up interviews. Following discontinuation of study medication, reporting rates of withdrawal adverse events were 10.4% for mirtazapine, placebo 14.3%, and active control 26.2%. In the short term studies, signs and symptoms that could be considered withdrawal related occurred in 6/170=3.5% mirtazapine and 8/106=7.5% placebo subjects. In the long term studies 12/141=8.5% mirtazapine and 2/34=5.9% placebo patients reported signs and symptoms that could be considered withdrawal related.

In addition, the sponsor does not report any instances of mirtazapine abuse or dependence. There was lack of voluntary and persistent dose escalation by patients, and few reports of euphoria. Overall, there seems to be no evidence of withdrawal phenomenon or abuse potential for this drug.

8.5.9 Human Reproductive Data

Pregnancy was an exclusion criterion for enrollment and when a patient became pregnant they were discontinued. Of the eight patients who became pregnant in the phase II-III studies, six were in the Org 3770 group while two were treated with active controls.

Two healthy live births were reported for patients who took Org 3770, patients #921 [Study 003-010] had been in the study for 62 days and it was estimated that she had been pregnant for 5-6 weeks before discontinuation, and #066 [Study 003-026] had been in the study for 625 days and it was estimated that she had been pregnant for 3 weeks before discontinuation. Three pregnancies ended in abortions, and patient #942 [Study 003-010] had a false positive pregnancy test. Two pregnancies were reported for patients who took active control compounds, patients #055 [Study 003-027] and #074 [Study 85003], both pregnancies were uneventful and resulted in the births of normal healthy babies.

8.5.10 Overdose Experience

During the worldwide development of Org 3770 there were 18 attempted overdoses of which 8 involved Org 3770 alone or in combination with other drugs. There were no overdose deaths associated in the Org 3770 alone cases, however one patient (study 84023, # 112) died from a combination overdose of Org 3770, amitriptyline and chlorprothixene. The overdoses cases involving Org 3770 are listed below:

Patient # 110 (study 003-010), a 31 year old female attempted suicide by Org 3770 overdose (300 mg) on day 153 of study. The only adverse event reported was sedation.

Patient # 421 (study 003-010), a 27 year old male attempted suicide by Org 3770 (975 mg) and clonazepam (30 mg) overdose on day 339 of study. His Org 3770 overdose was 22 fold the prescribed dose and the clonazepam was 30 fold higher (no plasma levels are recorded or mentioned in the patient narrative or CRF). He was disoriented, drowsy (lasting 16 hours), had impaired memory and also experienced transient increase in heart rate.

Patient # 112 (study 84023), a 47 year old female died due to overdose with Org 3770, amitriptyline and chlorprothixene on day 13 of study. She was inpatient then sent home for the weekend. After the weekend she phoned the hospital complaining of nausea and flu-like symptoms, but failed to come to the hospital. She was later found dead in her apartment. An autopsy of this patient revealed toxic levels for amitriptyline (1 mg/l) and chlorprothixene (2.5 mg/l), while the Org 3770 level was 2-3 fold the therapeutic levels produced by normal dosing (actual level not recorded). In this reviewer's opinion the death is attributable to TCA toxicity rather than mirtazapine.

In addition to the above, there were several overdoses with uneventful recoveries and no adverse events reported during the overdose:

Patient # 746 (study 003-010), a 29 year old female attempted suicide by Org 3770 overdose (estimated 354 mg) on day 19 of study.

Patient # 283 (study 85002), a 43 year old female attempted suicide by Org 3770 overdose (100 mg) on day 35 of study.

Patient # 98 (study 85003), a 37 year old female attempted suicide by Org 3770 and oxazepam overdose (amount unknown) on day 171 of study.

Patient # 21 (study 85027), a 36 year old female attempted suicide by Org 3770 (150 mg) and pain killer overdose on day 34 of study.

Patient # 44 (study 85146), a 22 year old female attempted suicide by Org 3770 (180 mg) overdose on day 31 of study. 2 hours after ingestion the plasma drug level was 49.9 ng/ml.

On July 18, 1995 the sponsor submitted a sketchy adverse events report regarding European study 86017. A female patient took an overdose of mirtazapine (810 mg) with plasma levels reaching 206 ng/ml; she was hospitalized for confusion. She recovered without sequelae in one day. There were no ECG, vital sign or laboratory abnormalities.

On 9/14/95 the sponsor submitted "Data from Spontaneous Reporting" from the Postmarketing Surveillance in the Netherlands, and in this report there are 3 overdoses mentioned:

1. An 81 year old female took an overdose of 60 tablets of 15 mg mirtazapine and 14 tablets of 15 mg midazolam. Patient was admitted to the intensive care unit in a subcomatose state but regained consciousness in few hours. There were no ECG or other abnormalities reported. She was placed back on mirtazapine 4 days later.
2. A female of unknown age took an overdose of 27 tablets of 30 mg mirtazapine. Mirtazapine plasma level of 205 mcg/liter was measured. Patient was anxious and delirious. There were no ECG or other abnormalities reported. Patient had fully recovered the following day.
3. A 23 year old female took an overdose of 15 tablets of 30 mg mirtazapine and unknown amount of alcohol. Two hours after the suicide attempt she felt drowsy. Patient recovered without sequelae.

Overall, except for the fatal overdose also involving amitriptyline, there were a lack of clinically serious symptoms in patients with Org 3770 overdose. The symptoms reported, even at the highest dose (22 fold the prescribed dose) included disorientation, drowsiness, impaired memory, and increased rapid heart rate with all the symptoms resolving promptly and without intervention.

8.6 Summary of Important Adverse Events Considered Possibly or Probably Drug Related

8.6.1 Somnolence/Sedation

Somnolence/sedation accounted for premature discontinuation in 218/2796=7.8% of mirtazapine treated patients, in 10/605=1.65% of placebo, and in 68/1161=5.86% of active control treated patients. It should be noted that all complaints of drowsiness, grogginess, sedation, sleepiness and somnolence are included under the heading of somnolence/sedation. Again, as with other adverse events, the vast majority of premature terminations come from US studies. Somnolence/sedation was severe enough in many patients that it interfered in their daily activities and contributed to motor vehicle accidents (MVA) in some:

Patient #253 (study 003-010) was prematurely terminated from the study after she experienced a minor MVA. Her sedation started at day 2 of dosing and was disabling, especially at work. On day 23 she had the accident and her medication (15 mg of mirtazapine)

was stopped for three days. It was resumed at half the dose, but on day 28 the investigator thought it best for the patient to discontinue from the study.

Patient #514 (study 003-010) also experienced an MVA, but the circumstances of the accident (patient was rear-ended) made it not likely that it was secondary to drug related sedation.

Patient #609 (study 003-010) was prematurely terminated due to sedation after five days on study medication (7.5 mg of mirtazapine). She experienced increased sedation starting on day 3, also complained of "drowsiness, fogginess in thinking, and blurred vision. While on medication she had an MVA, which she attributed to her fogginess in thinking and blurred vision.

Patient #124 (study 003-020) a non-compliant 24 year old female experienced a minor MVA after four days on study medication (5-20 mg of mirtazapine/day). She experienced sedation while on medication, but direct relationship to MVA and sedation is not clear.

In the short term placebo controlled US studies somnolence was reported with 53.6% incidence in the mirtazapine patients, 18.0% with placebo, and 59.6% with Amitriptyline. These incidence rates were similar for the remaining database as well. 40% of the patients report somnolence by week 1, occurrence rates gradually decreasing thereafter, with no evidence of building tolerance. No age, gender, or dose related differences in reporting were found. It is clearly evident that sedation is a major side effect that can be ascribed to mirtazapine.

An analysis of adaptation of this very common adverse event did not reveal any adaptation:

Somnolence	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6
Org 3770 N = 116	100%	78%	64%	62%	56%	47%
Placebo N = 21	100%	95%	86%	76%	62%	52%

8.6.2 Hepatotoxicity

Overall, 26 patients (26/2796=0.93%) treated with mirtazapine were prematurely terminated or experienced a serious event due to increases in one or more liver enzymes, including GGT, alkaline phosphatase, LDH, ALT (SGPT), and AST (SGOT). (There was only 2 (2/1161=0.17%) in the active control group and 2 (2/605=0.33%) in the placebo group).

There seems to be cause and effect relationship between administration of mirtazapine and liver enzyme elevations, without any specific factors such as age, sex, dose or duration of exposure that predispose an individual for liver enzyme elevation. Statistically significant increases in liver enzymes

were seen in the short-term US studies. As a risk factor for hepatotoxicity, concomitant ingestion of alcohol stands out.

The post-marketing reporting (up to mid 1994) of mianserin, the sister compound to mirtazapine, with an exposure of 3.2 million patient years, reveals a frequency of hepatic function abnormalities of 115 cases, hepatitis 22 cases and cholestatic hepatitis 22 cases.

In summary: The serious, but rare adverse events of chemical hepatitis and the more common occurrence of hepatic liver enzyme elevations can be causally ascribed to mirtazapine. Despite the apparent causal relationship, the liver enzyme elevation is modest and transient in the vast majority and resolves completely without sequelae. My recommendation is baseline and periodic evaluations of liver function and avoidance of its use in patients with liver disease and alcohol abuse.

8.6.3 Agranulocytosis/Neutropenia

Overall, 13 patients ($13/2796=0.46\%$) treated with mirtazapine were prematurely terminated and/or experienced a serious adverse event due to leukopenia and/or neutropenia, including three agranulocytoses (one being pancytopenia with agranulocytosis). (There were $2/605=0.31\%$ (leukopenias) in the placebo group and $3/1161=0.26\%$ (leukopenias) in the active control group. In addition there is one agranulocytosis case in the active control group in the ongoing European study, not part of this database).

Considering the above, the discrepancy in incidences of serious adverse events and premature terminations due to hematologic adverse events between mirtazapine and placebo and the statistically significant mean changes (decreases) of neutrophils and bands (appendix 8.5.2.2.1) in the short term US controlled studies, it is reasonable to ascribe a cause and effect relationship between the administration of mirtazapine and decreases in WBC and neutrophils.

To put this in perspective it is worthwhile to compare the developmental phases of mirtazapine and felbamate. The clinical review of the felbamate NDA (approved Aug 1993) and the retrospective hematology consult prepared for the advisory committee (Sep 27, 1994) on the postmarketing reports of aplastic anemia, reveal similarities to mirtazapine. In the felbamate clinical trials (Phases II-III) total number of patients exposed to the drug was 1677 (1246 adults and 431 pediatric patients). No cases of aplastic anemia were reported, although after marketing it was determined that felbamate caused aplastic anemia. In Phases II and III, compared to placebo and valproate a statistically significant decrease in WBC occurred in the felbamate group, especially when felbamate was used as adjunctive therapy and not as monotherapy. No decreases of hemoglobin and hematocrit or platelet decreases were seen. An overall analysis of the database revealed that 15 patients had $ANC < 1,000$ while on felbamate (most declines seen at one visit only), with counts improving as other drugs were discontinued and felbamate was used as monotherapy. Overall, there were 5 premature terminations due

to neutropenia three of them with ANC's of 35, 420, and 459.

To better understand the worrisome hematologic and chemistry adverse events in Org 3770 treatment groups, a look at the post-marketing experience with mianserin, the sister compound to mirtazapine, is necessary.

Mianserin is a tetra-cyclic compound first synthesized in 1966 and developed in Europe since 1969 by Organon International. Mianserin was first introduced on the world market in 1974 by Organon and an IND was submitted to the agency in 1977 under IND # 13,400. It is a piperazine-dibenzazepine with marked antihistaminic and antiserotonergic properties and little or no action on reuptake of amines. It differs structurally from mirtazapine by one nitrogen atom.

On December 2, 1994 the sponsor submitted a summary of "Spontaneous adverse drug effects (ADE) reports on Tolvon[®]," as part of this NDA. This summary encompasses all ADEs reported from the initial introduction of this drug to the end of 1993. There is a total of 2,430 reports with 3,469 ADEs associated with the use of mianserin. Among the total number of 2,430 ADE reports, 95 reports (4%) had a fatal outcome.

From 1974 onwards, mianserin has been marketed in over 70 countries, and the extent of its use is estimated on the basis of NV Organon sales figures. Based on sales in number of defined daily doses (DDD) per year, the cumulative total amount of mianserin sold world-wide is approximately 1.17 billion daily doses. Of greatest concern regarding the ADEs are the 445 reports on blood dyscrasias including 38 fatalities received through Jan. 1, 1994. These 445 ADEs are broken down into the following diagnoses: leukopenia-73 cases with 2 fatalities; granulocytopenia-114 cases with 3 fatalities; agranulocytosis-231 cases with 20 fatalities; pancytopenia-27 cases with 13 fatalities. The total represents a reporting rate of 0.38 per 10⁶ DDDs of mianserin use. To get a better understanding of the reporting rate I converted the analysis given by the sponsor to reflect a reporting rate in patient years: the 1.17 billion DDS is equivalent to 3.2 million (1.17 billion/365) patient years; and 445 cases of blood dyscrasias reflect 139 cases of blood dyscrasias per million patient years.

My presentation above summarizes overall reporting rates. When comparing reporting rates from specific countries, there are wide disparities, for example New Zealand and Sweden report much higher rates than other countries such as Belgium or UK. Further analysis of the reported cases reveals no correlation between the gender and blood dyscrasias while on mianserin, but there seems to be an influence of age with the elderly having a higher reporting. There was no clear dose response relationship to the development of blood dyscrasias, but the most common time for the development is between 4-6 weeks of treatment, while only 10% of cases occurred after 3 months of use. We have to assume that there are cases that are not reported, and it is possible that late onset cases are not as frequently reported. Most (66%) recovered within two weeks of treatment discontinuation.

An additional report of mianserin postmarketing ADEs covering the period of 1/1/94-7/1/94 reveals additional 10 cases of blood dyscrasias including 5 agranulocytoses.

In summary: The serious adverse events of agranulocytosis (with an estimate of crude incidence rate of 1/1000), pancytopenia, and the more common occurrences of neutropenia and leukopenia can be causally ascribed to mirtazapine. The well known hematologic adverse events of mianserin, in particular leukopenia and agranulocytosis and mirtazapine's chemical similarity to mianserin make it more than likely that mirtazapine will have hematologic toxicity. The agencies external consultant Dr. Lewis Weintraub, the sponsor's consultant Dr. Stanton Gerson and the PDAC did not recommend monitoring of the WBC. This assessment is based upon the evaluation that the expected rate of agranulocytosis is very low and there seem to be no gradual decline of the neutrophil count to warn of the impending event.

8.6.4 Fat Metabolism And Weight

There is also compelling evidence that mirtazapine has a tendency to elevate cholesterol and triglyceride levels: in short term placebo controlled US studies the incidence of clinically significant (20% above normal limits) elevation in cholesterol levels was 15% in mirtazapine patients compared to 7% in placebo (a statistically significant difference), and 8% for amitriptyline. Considering that mirtazapine also causes weight gain and increased appetite, the elevation of cholesterol and triglyceride levels may be a secondary effect of overeating. This is specially the case because the cholesterol and triglyceride samples were not fasting levels. In non-US studies many patients were inpatients and hence with tightly-controlled diets, perhaps leading to a lower percentage of patients with cholesterol and triglycerides elevations. The combination of weight gain and cholesterol level elevation may increase the index of risk factors predisposing to cardiovascular disease.

Weight gain is one of the most frequently reported adverse events. 107 (107/2796=3.81%) patients treated with mirtazapine were prematurely terminated due to weight increase. As appendix 8.5.3.1 shows, there is statistical significance (at $p \leq 0.05$) for clinically significant weight gain (>7% from baseline weight), when comparing mirtazapine to placebo.

It is apparent that weight gain is a common and significant adverse event with clear causal relationship to the study medication. The continued weight gain with continued exposure, and the triglyceride and cholesterol elevations in conjunction with the weight gain, may place an individual at a higher long-term risk for cardiovascular complications.

8.6.5 Cardiovascular

Org 3770 induced a statistically, but not clinically significant mean increase in heart rate (3.38 bpm) and QTc interval (4.3 msec) compared to placebo. The amitriptyline-induced increase in heart rate (13.33 bpm) and QTc interval (17 msec) was

significantly greater.

The frequent episodes of orthostatic hypotension and exaggerated vasovagal responses experienced in the Phase I studies can be directly linked to the study drug. The two cases described in section 8.5.4 (patients #006, study 88005 and #028 study 22503) are illustrative of this fact.

In summary, when evaluating cardiovascular adverse events and ECG abnormalities, it is apparent that normal healthy volunteers are susceptible to orthostatic hypotension, exaggerated vasovagal episodes and, with IV dosing, possible cardiac arrest. In Phase II-III studies the orthostatic hypotension and exaggerated vasovagal responses were not nearly as prominent as in Phase I. 7 patients ($7/2796=0.25\%$) treated with mirtazapine were prematurely terminated due to Vital Signs related (excluding Weight) adverse events, all due to increases or decreases in blood pressure.

It appears that this patient population is not nearly as susceptible to the adverse effects (orthostatic hypotension and exaggerated vasovagal responses) that afflicted the normal healthy volunteers. In the Phase II-III studies, there are indications that mirtazapine may have cardiotoxic effects: an influence on the conduction pathway (as evidenced by 2 cases of LBBB) and the statistically significant prolongation of QTc and increased heart rate. However, Org 3770 overdose appears to have relatively benign cardiovascular effects. It is difficult to assess Org 3770's potential cardiovascular adverse effects but they may be important for certain susceptible patients.

8.6.6 Seizures

In the integrated safety data set, convulsions occurred in only one ($1/2796$) mirtazapine patient (# 91, Study 84072) and in three active control patients (doxepin # 75, Study 85003 and amitriptyline # 135 and 213, Study 85146). This indicates that mirtazapine is not a pro-convulsant.

8.7 Important Events Considered Not Drug Related

The definition of a serious adverse event is given above in section 8.4.2. Appendix 8.7.1 displays a listing of such adverse events for mirtazapine that in this reviewer's opinion are not attributed to treatment. Please note that fatalities have already been included in Appendix 8.2 and are not repeated in Appendix 8.7.1.

8.8 Summary of Drug Interactions

8.8.1 Drug-Demographic Interactions

The sponsor performed one US study to assess the effects of age on the pharmacokinetics of Org 3770:

Study # 003-006 was an open-label, non-randomized, single and multiple dose, parallel-group study of 20 adults (18-65) and 20 elderly (>65) volunteers. The study was designed to compare the

pharmacokinetics of Org 3770 (20 mg) in the two age groups. All treatment groups reached steady state after 7 days of chronic administration of 20 mg of Org 3770 daily. The $C_{ss,min}$ and AUC were significantly higher in the elderly group with a decrease in clearance of 40%. The same parameters were also significantly higher in females than in males with a decrease in clearance of 45%. The mean for $C_{ss,min}$ and AUC after multiple dosing were higher than after single dosing. The division of Biopharmaceutics performed the analysis normalizing for weight and the differences held up.

No particularly different or severe adverse events were reported in the different groups. It appears that there are gender and age related differences on the pharmacokinetics of Org 3770 and dosing titrations in the elderly should be done with particular care.

Differences in adverse events on the basis of age and gender are discussed in section 8.5.1.3.

8.8.2 Drug-Disease Interactions

The sponsor performed two Non-US studies to explore drug-disease interactions.

Study # 22503 was an open-label, single-dose (15 mg) study designed to assess the effects of different stages of Renal Impairment on the pharmacokinetics of Org 3770 in forty volunteers divided into four groups of five male and five female subjects differentiated on the basis of their glomerular filtration rate (GFR). There was no evidence that subjects with advanced renal impairment tolerated the single oral dose of Org 3770 less well than those with normal renal function. Two subjects with mild renal insufficiency experienced syncope. The AUC is increased and the clearance decreased by 30% for patients suffering from moderate (GFR 11-39) and by 50% from severe (GFR <10) renal insufficiency when compared to normal controls (GFR >80) and those with mild insufficiency (GFR 40-79). It will be prudent to decrease dosing of renally impaired patients by 50% to avoid accumulation of the drug.

Study # 88007 was an open-label, single-dose (15 mg) study designed to assess the influence of Hepatic Impairment on the pharmacokinetics of Org 3770 in 8 elderly volunteers with mild to moderate hepatic disease and 8 control subjects. The clearance was decreased by 33%, elimination half-life increased by 40%, and AUC increased by 57% in the hepatic disease group compared to the controls. The rate of absorption (C_{max} and T_{max}) were not affected. The two side effects reported were hypotension and sedation, with evidence that subjects with hepatic impairment had more pronounced and prolonged symptoms.

8.8.3 Drug-Drug Interactions

The sponsor performed three Non-US studies to explore interactions of mirtazapine with other drugs:

Study # 85147 was a double-blind, placebo-controlled, 4 way cross-over alcohol interaction study. The study was designed to detect pharmacodynamic effects of Org 3770 (15 mg) alone and in combination with ethanol (60 g) in eight healthy male volunteers, both after acute and subchronic dosing.

Org 3770 had significant sedative effect after acute administration both alone and in combination with ethanol. The sedative properties were broadly additive with individual supersensitivity to this interaction detected: 2 individuals prematurely terminated due to adverse events (one for extreme sedation and the other for profound postural hypotension) after acute exposure to the combination.

Study # 85148 was a double-blind, placebo-controlled, single-dose cross-over/amitriptyline diazepam interaction study. The study was designed to detect pharmacodynamic effects of Org 3770 (15 mg) and amitriptyline (50 mg) alone and in combination with diazepam (15 mg) in 12 healthy male volunteers. Concomitant administration of Org 3770 and diazepam had no significant effects on the plasma levels of either drug, but there were significant skilled performance decrements and increased sedation and orthostatic changes. The effects were additive.

Study # 88043 was an open label, single dose alcohol interaction study. The study was designed to determine the effects of Org 3770 (15 mg) in combination with ethanol (30 and 45 g) in 4 healthy male volunteers. The study was prematurely terminated when one of three volunteers exposed to 15 mg of Org 3770 and 45 g ethanol developed excessive sedation and severe postural hypotension 110 min after ingesting Org 3770 and 80 min after ingesting ethanol. The symptoms lasted 7.5 hrs.

From these three studies and from the safety review in the chemistry section, it is apparent that patients should avoid concomitant use of mirtazapine and alcohol. At the initiation of therapy, the evidence points to an additive effect of the two compounds in inducing excessive sedation and severe postural hypotension, but synergistic effects can not be ruled out. With chronic usage there is some evidence of added risk of increased liver enzyme elevations with exposure to alcohol. Concomitant use of mirtazapine and benzodiazepines should be avoided as well, because of the additive pharmacodynamic effects of the two.

9.0 Labeling Review

The clinical and pharmacokinetics section of the proposed labeling for Remeron have been examined. Following are the significant findings of that review:

Pharmacokinetics:

In the proposed labeling there is no mention of the enzymes involved in the metabolism of Remeron. Complementary data (such as inhibition study results) should also be included.

Indications and Usage:

The sponsor's proposed labeling states:

1. "Remeron has been shown to reduce anxiety." Further prospective studies may be necessary to insert such statements in the labeling.
2. "The efficacy of Remeron in maintaining an antidepressant response for at least one year has been demonstrated in long-term, placebo-controlled studies." While such studies have been conducted, they are not of adequate design to evaluate long-term efficacy. Here as well, further prospective studies are necessary to insert such statements in the labeling.
3. Another issue that deserves mention here is the lack of evidence for a dose-response relationship in the mirtazapine drug development process.

Warnings:

I agree that agranulocytosis should receive a special mention and be prominently displayed in this section.

Precautions:

Somnolence: There should be special mention of hazards of driving while under therapy, since there does not seem to be adaptation to this adverse event.

Liver enzyme elevations: I agree that this should receive a special mention and be prominently displayed in this section.

Use in patients with concomitant illness: I would recommend changing the sponsor's proposed labeling to state that use of the drug should be avoided in patients with moderate to severe liver disease.

Drug Interactions: I agree that patients on Remeron should avoid alcohol use and concomitant therapy of sedating drugs like diazepam.

10.0 Conclusions

In my opinion, the sponsor has demonstrated the efficacy of mirtazapine (RemeronTM) in the short-term treatment of major depression.

There are several safety concerns with the use of this drug, most worrisome being agranulocytosis. Others include liver enzyme elevations, somnolence/sedation, weight gain and cholesterol and triglyceride elevations. While these adverse events may place a patient at risk, the incidence rates for the occurrence of the serious adverse events are felt to be exceedingly low. A conservative approach (such as monitoring of liver enzymes and/or hematology values) was advocated by this reviewer and our internal consultants in general, however it was the opinion of the PDAC and the sponsor's consultants that these safety concerns did not warrant such special attention during the regular use of mirtazapine. Their assessment was that these events were rare and not predictable even with monitoring.

11.0 Recommendations

In my opinion, the New Drug Application for Mirtazapine is approvable from a clinical standpoint. However, to further support the safe and effective use of mirtazapine, it is

recommended that the following issues be explored by the sponsor:

1. The long-term efficacy of mirtazapine in the treatment of major depression be examined by an adequate trial of at least one year duration, such as a relapse prevention trial.
2. More fixed-dose studies should be conducted to elucidate the dose-response relationship in major depression, particularly to identify the minimum effective dose.
3. Adequate drug-drug interaction studies to elucidate the inhibition characteristics of the drug for the P450 enzymes (2D6 and 3A).
4. An adequate surveillance procedure (by sponsor or agency) to capture all potential reports of agranulocytosis.
5. Clinical trials in pediatric populations.

John Dikran Balian, M.D.

John Dikran Balian, M.D.
Clinical Reviewer,
Div. of Neuropharmacologic Drug Products

10/19/1995
Date

Orig. NDA 20-415
HFD-120 Div. File
HFD-120 TLaughren\AMosholder\PDauid\JBalian

10-21-95

*I agree that this NDA is
approvable. My summary of the data
and more detailed comments &
recommendations will follow in
a memo to the file.*

James P. Laughren, MD
GL, PDP

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**APPENDIX 1.1.1
ITEMS REVIEWED**

Submission Date	NDA Volume # (IND Amendment #)	Material Reviewed
06/21/82	---	Original IND
03/09/88	(011)	Copy of letter to investigators for case of thrombocytopenia
08/29/89	(055)	Response to FDA requests for information on hematological events
11/03/89	(064)	Response to FDA request for hematologic safety information
03/21/90	(072)	Correspondence - hematologic issues
04/29/94	2.1 - 2.2 2.3 2.65 - 2.66 2.195 2.196	Overall Table of Contents Application Summary Clinical Technical Summary (2 volumes) Integrated Summary of Effectiveness Integrated Summary of Safety
06/08/94	---	Listing of protocol and protocol amendments for Phase II and Phase III studies.
06/22/94	---	Listing of prematurely terminated patients.
07/01/94	(091)	Annual report
09/21/94	---	Minutes to the pre-NDA meeting of 7/22/94.
11/10/94	---	Premature discontinuation summaries
12/05/94	(092)	Safety report
12/20/94	---	Pregnancy summary
12/21/94	---	CRF for Patient #0326 from Study 003-010.
12/27/94	---	Patient listings of adverse experience.
12/27/94	---	Urinalysis summary
12/29/94	---	Ophthalmology summary
12/29/94	---	Reanalysis of efficacy parameters ("Efficacy Addenda")
12/29/94	---	Patient listings for prematurely terminated patients from Phase II and III studies.

Submission Date	NDA Volume # (IND Amendment #)	Material Reviewed
12/29/94	Vol. CRF 1-9 Vol. PN 1-7	Overall index of narratives and CRFs; Non-US CRFs for prematurely discontinued patients (Vols. CRF 1-19). US and non-US patient narratives from Phases I,II,III (Vols PN 1-7).
01/24/95	—	ECG report
01/26/95	3.1-3.9 3.1,3.2 3.3 3.3 3.8	Resubmission of NDA 20-415 Index Annotated Package Insert Foreign Marketing History Draft Package Insert
03/08/95	(093)	Safety Report
04/04/95	—	Human Pharmacokinetic and Bioavailability Summary on hard copy and diskette.
04/19/95	One Volume	-History of Material Submitted to the Agency.
5/8/95	One Volume	-Revised Tables (demographics, dosage and exposure), hard copy and diskette.
6/29/95	One Volume	-Revised Safety Tables, hard copy and diskette.
7/28/95	One Volume Two Volumes Four Volumes	-Efficacy Synopsis with tables of 11 studies, hard copy and diskette. -Hematology package (Absolute Neutrophil Count: analysis) -Safety Update
8/21/95	One Volume	-Revised Draft Package Insert -Premature termination Table -Baseline P-Value (11 Efficacy Studies)
9/13/95	One Volume	-Risk Ratios for age and gender -Postmarketing Data from Spontaneous Reporting
9/14/95	Three Volume	-Hematology updated package (Absolute Neutrophil Count analysis)

APPENDIX 1.1.2
Case Report Forms Reviewed

Study	Patient	Drug	Study	Patient	Drug	Study	Patient	Drug
003-010	671	Org	003-010	124	Org	003-010	936	Org
85146	224		85146	173		003-023	69	Pbo
85003	168		85042	24	Amit	003-010	841	Org
86017	46	Imip		147			645	
003-010	1010	Org	85031	9	Traz		532	
	1024		85003	137	Dox		424	
	167		003-008	29	Pbo		569	
	837		003-010	1051	Org		227	
	217		003-003	29		003-020	095	
	248		003-010	137		003-023	129	
	408			283		003-027	001	
	416			219			079	
	420			392		003-022	144	Amit
	664			842		003-026	40	
003-020	61		85031	172		003-023	76	Traz
	84		003-010	858		22503	028	Org
003-003	67			908		88005	6	

APPENDIX 5.1.1 TABLE SUMMARY OF ALL STUDIES

Phase 1 Safety and Dose Tolerance Studies

Single Dose:		
Study No.: None SDGRR No.: 857	Open-label, single rising-dose safety and tolerance study, normal female volunteers (n=2 in each of three treatment groups), Org 3770: 0.5 and 10 mg; 2 and 25 mg; 5 and 35 mg with a 5 day drug-free period inbetween.	
Study No.: 01430 SDGRR No.: 1430	Randomized, double-blind, placebo-controlled, single rising-dose tolerance study, normal male volunteers (n=10), 1 placebo followed by Org 3770 (0.1, 1 and 5 mg) with 2 drug-free days between each dose.	
Study No.: 85150-3 SDGRR No.: 3387	Double-blind, placebo-controlled, cross-over, single dose tolerance study, normal male volunteers (n=4), Org 3770 single dose (20 mg oral or 0.1 mg/kg IV) followed by placebo single doses (IV and oral).	
Study No.: 86020 SDGRR No.: 2084, 2167	Randomized, double-blind, placebo-controlled, single rising-dose tolerance study of 14 to 17 days duration, normal male volunteers (n=12, placebo = 4), Org 3770 doses (30, 45, 60, and 90 mg), placebo doses (6 and 9 tabs).	
Subchronic Dose:		
Study No.: None SDGRR No.: 1333	Open-label, fixed-dose study, Org 3770 dose (15 mg X 10 days); normal female volunteers (n=7).	
Study No.: 22505 SDGRR No.: 3307,3308, 3309, 3332	Randomized, double-blind, placebo-controlled, multidose study, normal male volunteers (n=6, placebo=2), Org 3770 dose (3.5 mg IV on Days 1, and 3-5; 7 mg IV on Days 6-12); placebo dose (IV).	
Study No.: 82007 SDGRR No.: 1457	Double-blind, placebo-controlled, cross-over, plasma concentration study, normal male volunteers (n=12), Org 3770 dose (20 mg single dose) followed by 10 mg (bid) X 1 week.	
Study No.: 87003 SDGRR No.: 2084, 2166	Randomized, double-blind, placebo-controlled, single rising-dose safety and tolerance study. Normal male volunteers (n=6, placebo=2). Org 3770 doses: 15 mg/d on Days 1-4, 30 mg/d Days 5-8, 45 mg/d Days 9-11.	
Study No.: 88005-1 SDGRR No.: 3386	Open-label, two-way cross-over, single and multidose drug-tolerance study, normal male volunteers (n=6), Org 3770 dose (15 mg single oral dose combined with a 7 mg IV dose ¹³ C-Org 3770 - day 1, followed by 5 drug-free days, then 15 mg/d oral dose x 6 days and a 15 mg. oral dose combined with a 3.5 mg IV dose of ¹³ C-Org 3770 on Day 7).	

APPENDIX 5.1.1 TABLE SUMMARY OF ALL STUDIES (CONTINUED)

Phase I Studies

Pharmacodynamic Studies (Continued)

Single Dose:	
Study No.: None SDGRR No.: 3420	Single-blind, placebo-controlled, cross-over EEG study, comparing two single doses of the enantiomers of Org 3770; normal male volunteers (n=16); dose [(+) enantiomers (0.5 and 1.0 mg) and (-) enantiomers (0.5 and 1.0 mg)].
Study No.: None SDGRR No.: 3421	Cross-over, placebo-controlled, single dose EEG study; normal male volunteers (n=6); Org 3770 dose (2 mg).
Study No.: 86021-1 SDGRR No.: 3485	Double-blind, cross-over, placebo-controlled, single dose study of the effects of Org 3770 on melatonin secretion; normal male (n=9) and female (n=1) volunteers, Org 3770 dose (30 mg); placebo dose (1 tab).
Study No.: 86022-1 SDGRR No.: 3452	Double-blind, cross-over, placebo-controlled study of the effects of single doses of Org 3770 or placebo on pupil-diameter changes brought about by tyramine, phenylephrine, and pilocarpine eyedrops (15 µL) administered 2 h after Org 3770 or placebo ingestion. Normal male (n=8) and female (n=3) volunteers; Org 3770 dose (30 mg) was given on three occasions and placebo was given on three occasions with 1-week intervals between treatments.
Study No.: 87024 SDGRR No.: 2339	Double-blind, cross-over, placebo-controlled, EEG study; normal male volunteers (n=6); a single-dose of Org 3770 dose (30 mg) on two occasions 13-days apart.
Study No.: 87027 SDGRR No.: 3419	Open-label, single rising-dose study, Org 3770 doses (15 and 30 mg); normal male volunteers (n=2).
Subchronic Dose:	
Study No.: 88006-1 SDGRR No.: 3554	Open-label, single-center, 4-week, conducted to evaluate the effects of Org 3770 on melatonin secretion in inpatients with major depression (n=4); Org 3770 dose 30 mg/d x 7 days followed by 45 or 60 mg/d, bid, x 21 days).
Study No.: 88032 SDGRR No.: 3579	Double-blind, randomized, placebo controlled study with all patients on desipramine (2 mg/kg/day) for the 4 weeks prior to initiation throughout the period of Org 3770 or placebo or treatment. There were 7 patients (6 male and 1 female) in each of the two treatment groups.

APPENDIX 5.1.1 TABLE SUMMARY OF ALL STUDIES (CONTINUED)

Phase I Drug Interaction Studies

Drug-Drug Interactions:	
Study No.: 85147 SDGRR No.: 2507	Double-blind, placebo-controlled, 4-way cross-over, single and multiple dose, alcohol interaction study, normal male volunteers (n=8), Org 3770 dose (15 mg/d on Days 1-3 and Day 8; 30 mg/d on Days 4-7), ethanol dose (60 g/d on Days 1 and 8), placebo dose (1-2 tabs/d).
Study No.: 85148 SDGRR No.: 2468	Randomized, cross-over, double-blind, placebo-controlled, diazepam (15 mg) interaction study. Org 3770 (15 mg), amitriptyline (50 mg), and placebo were each administered once to 12 volunteers (5 females and 7 males).
Study No.: 88043-II SDGRR No.: 3464	Open label, single dose alcohol interaction study, normal male volunteers (n=3), 45 g of alcohol was administered 30 min after ingestion of a 15 mg dose of Org 3770.
Drug/Food Interactions:	
Study No.: 003-012 SDGRR No.: 3181	Randomized, open-label, two-way cross-over, single dose, fasting vs. fed study, normal male volunteers (n=20), Org 3770 dose (15 mg).
Drug-Disease Interactions:	
Study No.: 22503 SDGRR No.: 3163, 3162, 3164	Open-label, single-dose PK study, normal volunteers (n=10), renal patients (n=30); Org 3770 dose (15 mg).
Study No.: 88007 SDGRR No.: 2992	Open-label, single-dose PK study, normal male volunteers (n=8), male patients with mild to moderate hepatic disease (n=8), Org 3770 dose (15 mg). All participants in the study were > 60 years-of-age.
Drug-Demographic Interactions:	
Study No.: 003-006 SDGRR No.: 2168, 3562	Non-randomized, open-label, parallel group, single and multiple dose PK study, normal male and female adults and geriatric (age: 65-74) volunteers (n=40 total), Org 3770 dose (20 mg single dose) followed by a 5-day drug-free period and then 20 mg/d on Days 6-12).

APPENDIX 5.1.1 TABLE SUMMARY OF ALL STUDIES (CONTINUED)

Phase 1 PK Studies

Single-Dose:	
Study No.: None SDGRR No.: 1451	Open label, single dose PK study, normal male volunteers (n=3), Org 3770 dose (5 mg).
Study No.: 22501 SDGRR No.: 3136,3135	Open-label, single dose PK study, normal male volunteers (n=6), Org 3770 dose (15 mg).
Study No.: 88003 SDGRR No.: 2499	Randomized, 4-way cross-over, single dose bioequivalence study comparing four different dose formulations (1 x 30 mg tab; 2 x 15 mg tab; 6 x 5 mg tab; and 6 x 5 mg caps), normal male volunteers (n=24).
Subchronic Dose:	
Study No.: 003-011 SDGRR No.: 3563	Open-label, single rising dose PK study, normal male volunteers (n=30), Org 3770 dose range (15-75 mg/d x 30 days). The dose was escalated from 15 to 75 mg/d in 15 mg intervals every 5 days.
Study No.: 84009 SDGRR No.: 1702	Open-label, single and chronic dose PK study, normal male (n=4) and female (n=4) volunteers, Org 3770 dose (20 mg single dose followed by a drug-free period of 4 days then 20 mg/d x 7 days).
Study No.: 85138 SDGRR No.: 2290	Open-label, single dose PK study, normal male (n=3) and female (n=3) volunteers, Org 3770 (20 mg/d x 14 days).
Study No.: 88001 SDGRR No.: 2550	Open-label, 2-way cross-over, single dose bioequivalence/PK study, comparing two different dose formulations. Normal male volunteers (n=20), Org 3770 doses (1 x 30 mg or 2 x 15 mg/d x 7 days).
Study No.: 88024 SDGRR No.: 2548	Open-label, single and chronic dose bioavailability study, normal male volunteers (n=8), Org 3770 dose (15 mg single oral dose combined with a 3.5 mg. IV dose - day 1, followed by a 4-day drug-free period - days 2-5, then 15 mg/d on Days 6, 7, 8, 9, 10 and 11; Day 12, a 15 mg single oral dose was combined with a 3.5 mg IV dose).

APPENDIX 5.1.1 TABLE SUMMARY OF ALL STUDIES (CONTINUED)

Phase II-III Efficacy and Safety Studies Placebo- and Active-Controlled

Short-Term Studies:	
Study No.: 003-020 SDGRR No.: 3220	Randomized, double-blind, single center, parallel group, active-(amitriptyline) and placebo-controlled, 6-week, 3-way flex-dose study, outpatients with major depression; Org 3770 dose range [(5-35 mg/d), n=44], amitriptyline dose range [(40-280 mg/d), n=43], and placebo [n=41].
Study No.: 003-021 SDGRR No.: 3283	Randomized, double-blind, single center, parallel group, active-(amitriptyline) and placebo controlled, 6-week, 3-way flex-dose trial, outpatients with major depression; Org 3770 dose range [(5-35 mg/d), n=50], amitriptyline dose range [(40-280 mg/d), n=50], and placebo [n=50].
Study No.: 003-022 SDGRR No.: 2528	Randomized, double-blind, single center, parallel group, active-(amitriptyline) and placebo-controlled, 6-week, 3-way flex-dose trial; outpatients with major depression; Org 3770 dose range [(5-35 mg/d), n=50], amitriptyline dose range [(40-280 mg/d), n=50], and placebo (n=50).
Study No.: 003-023 SDGRR No.: 3303	Randomized, double-blind, single center, parallel group, active-(trazodone) and placebo-controlled, 6-week, 3-way flex-dose trial; outpatients (≥ 55 years-of-age) with major depression; Org 3770 dose range [(5-35 mg/d), n=50], trazodone dose range [(40-280 mg/d), n=49], and placebo [n=50].
Study No.: 003-024 SDGRR No.: 2593	Randomized, double-blind, single center, parallel group, active-(amitriptyline) and placebo-controlled, 6-week, 3-way flex-dose trial; outpatients with major depression; Org 3770 dose range [(5-35 mg/d), n=50], amitriptyline dose range [(40-280 mg/d), n=50], and placebo [n=50].
Study No.: 84062 SDGRR No.: 3422	Randomized, double-blind, single center, parallel group, active-(Amitriptyline) and placebo-controlled study, 6-week, 3-way flex-dose trial; outpatients with major depression (n=15 in each of 3-treatment groups); Org 3770 dose range (20-80 mg/d), amitriptyline dose range (37.5-300 mg/d). The data for this study could not be verified and have not been included in the database.

APPENDIX 5.1.1 TABLE SUMMARY OF ALL STUDIES (CONTINUED)

Phase II-III

Efficacy and Safety Studies

Placebo- and Active-Controlled (Continued)

Long-Term: The studies listed on this page were identically designed. Patients were either continued on the same treatment that they had received during the short-term study [referred to as nonswitchers (NSW)] or they were switched to a different treatment if the investigator had declared that their short-term treatment was ineffective [referred to as switchers (SW)]. Patients were switched from placebo or amitriptyline to Org 3770 or from Org 3770 to amitriptyline. Patients in the NSW Group were maintained on placebo, but no patients were switched to placebo treatment.	
Study No.: 003-025 SDGRR No.: 3506	Randomized, double-blind, single center, parallel group, with NSW and SW groups as described above; 20 week + 24-week extension, outpatients with depression; Org 3770 dose range (5-35 mg/d), amitriptyline dose range (40-280 mg/d), placebo (1-7 caps/d). NSW (Org 3770=10; amitriptyline=9; and placebo=11) and SW (amitriptyline to Org 3770=12; placebo to Org 3770 =11; and Org 3770 to amitriptyline=9). Extension of study 003-020.
Study No.: 003-026 SDGRR No.: 3270	Same design as described for Study No. 003-025. NSW (Org 3770=21; amitriptyline=29; and placebo=19) and SW (amitriptyline to Org 3770=4; placebo to Org 3770 = 15; and Org 3770 to amitriptyline=18). Extension of study 003-021.
Study No.: 003-027 SDGRR No.: 3545	Same design as described for Study No. 003-025. NSW (Org 3770=27; amitriptyline=25; and placebo=17) and SW (amitriptyline to Org 3770=20; placebo to Org 3770=27; and Org 3770 to amitriptyline=15). Extension of study 003-022.
Study No.: 003-028 SDGRR No.: 3525	Same design as described for Study No. 003-025. NSW (Org 3770=16; amitriptyline=23; and placebo=10) and SW (amitriptyline to Org 3770=14; placebo to Org 3770=24; and Org 3770 to amitriptyline=17). Extension of study 003-024.

APPENDIX 5.1.1 TABLE SUMMARY OF ALL STUDIES (CONTINUED)

Phase II-III Efficacy and Safety Studies Placebo-Controlled Studies

Short-Term Studies:	
Study No.: 003-002 SDGRR No.: 3456	Randomized, double-blind, placebo-controlled, 6-week, flex dose parallel group study, single center, outpatients with major depression (n = 45 Org 3770 and n = 45 placebo), Org 3770 dose range (5-35 mg/d).
Study No.: 003-003 SDGRR No.: 3436	Randomized, double-blind, placebo-controlled, 6-week, flex dose parallel group study, single center, outpatients with major depression (n = 45 Org 3770 and n = 45 placebo), Org 3770 dose range (5-35 mg/d).
Study No.: 003-008 SDGRR No.: 3522	Randomized, double-blind, placebo-controlled, 6-week, fixed dose study, single center, outpatients with major depression (n=149 total); Org 3770 fixed doses (5, 15, 30, and 60 mg/d) and placebo dose (4 tabs/d).
Study No.: 82032 SDGRR No.: 3432	Double-blind, placebo-controlled, 42-day study, single center, female patients with major depression (n=2); Org 3770 (10 mg/d). No patients were treated with placebo in this study.
Study No.: 84008 SDGRR No.: 2240	Double-blind, placebo-controlled, 5-week, rising dose parallel-group study, single center, inpatients with major depression. The enantiomers of Org 3770 [Org 4419 dose range (20-60 mg/d), n=40; and Org 4420 dose range (20-60 mg/d), n = 40] were used but Org 3770 was not. Placebo (n=41).
Study No.: 84023 SDGRR No.: 2676	Randomized, double-blind, placebo-controlled, 6-week, flex dose multicenter study, inpatients with major depression; Org 3770 [dose range (15-50 mg/d); n = 59]] and placebo [n=55].
Study No.: 84050 SDGRR No.: 2334	Randomized, double-blind, placebo-controlled, 5-week, fixed-dose, single center, parallel group study, inpatients with major depression [n = 13 in each Org 3770 fixed dose (15, 30, and 60 mg/d)] groups. Placebo (n=12).
Study No.: 85027 SDGRR No.: 2694	Randomized, double-blind, placebo-controlled, 5-week, flex-dose, multicenter, parallel group study, inpatients with major depression; Org 3770 dose range [(20-60 mg/d), n=66] and placebo [n=66].
Study No.: 003-004 SDGRR No.: 3515	Double-blind, placebo-controlled, 7-week, flex dose, single center study, patients with major depression; Org 3770 dose range [(5-35 mg/d), n=10] and placebo [n=4]. Extension of study 003-002.
Study No.: 003-005 SDGRR No.: 3497	Double-blind, placebo-controlled, 7-week, flex-dose, single center study, patients with major depression, Org 3770 dose range [(5-35 mg/d), n=10] and placebo [n =5]. Extension of study 003-003.

APPENDIX 5.1.1 TABLE SUMMARY OF ALL STUDIES (CONTINUED)

Phase II-III Efficacy and Safety Studies Active-Controlled Studies

Short-Term Studies:	
Study No.: 82028 SDGRR No.: 2115	Double-blind, 4-week, multicenter, 3-way flex-dose study [Org 3770 (n=44), diazepam (n=47), and amitriptyline n = 48]], inpatients with psychotic or nonpsychotic depression; Org 3770 dose range (15-40 mg/d), amitriptyline dose range (75-200 mg/d) and diazepam dose range (15-40 mg/d).
Study No.: 83047 SDGRR No.: 2412	Double-blind, 6-week, multicenter, 2-way flex-dose study [Org 3770 (n=125) and amitriptyline (n=126)], inpatients with major depression; Org 3770 dose range (20-60 mg/d) and amitriptyline dose range (75-225 mg/d).
Study No.: 84072 SDGRR No.: 2361	Double-blind, 6-week, multicenter, two-way flex-dose study (Org 3770 and clomipramine), inpatients with major depression (n = 87 in each of 2 treatment groups); Org 3770 dose range (20-80 mg/d) and clomipramine dose range (50-200 mg/d).
Study No.: 85003 SDGRR No.: 2671	Double-blind, 6-week, multicenter, two-legged flex-dose study [Org 3770 (n=83) and doxepin (n=80)], inpatients with major depression; Org 3770 dose range (20-60 mg/d) and doxepin dose range (75-300 mg/d).
Study No.: 85004 SDGRR No.: 2577	Double-blind, 6-week, multicenter, two-way flex-dose study [Org 3770 (n=75) and maprotiline (n=74)], inpatients with major depression; Org 3770 dose range (20-80 mg/d) and Maprotiline dose range (50-200 mg/d).
Study No.: 85004-2 SDGRR No.: 3423	Randomized, double-blind, 28-day, single center, two-way flex-dose study [Org 3770 (n=7) and maprotiline (n=8)], inpatients with major depression; Org 3770 dose range (20-80 mg/d) and maprotiline (50-150 mg/d).
Study No.: 85031 SDGRR No.: 2693	Double-blind, 6-week, multicenter, two-way flex-dose study [Org 3770 (n=100) and trazodone (n=100)], inpatients with major depression; Org 3770 dose range (24-72 mg/d) and trazodone dose range (150-450 mg/d).
Study No.: 85042 SDGRR No.: 2692	Double-blind, 5-week, multicenter, two-way flex-dose study [Org 3770 (n=79) and amitriptyline (n=77)], inpatients with major depression; Org 3770 dose range (20-60 mg/d) and amitriptyline (75-225 mg/d).
Study No.: 85146 SDGRR No.: 2656	Double-blind, 6-week, multicenter, two-way flex-dose study [Org 3770 (N=103) and amitriptyline (n=104)], inpatients with major depression; Org 3770 dose range (20-60 mg/d) and amitriptyline (75-225 mg/d).
Study No.: 88013 SDGRR No.: 3148	Randomized, double-blind, 6-week, multicenter, two-way flex-dose study [Org 3770 (n=56) and amitriptyline (n=59)], elderly (age: 60-85) outpatients with major depression; Org 3770 dose range (15-45 mg/d) and amitriptyline (30-90 mg/d).

APPENDIX 5.1.1 TABLE SUMMARY OF ALL STUDIES (CONTINUED)

Phase II-III

Efficacy and Safety Studies

Active-Controlled Studies (Continued)

Long-Term Studies:	
Study No.: 85003 SDGRR No.: 3451	Double-blind, multicenter, (up to) 20-week extension, two-way flex-dose study [Org 3770 (n=20) and doxepin (n=8), inpatients with major depression; Org 3770 dose range (20-60 mg/d) and doxepin dose range (100-300 mg/d).
Study No.: 85146 SDGRR No.: 3700	Double-blind, multicenter, (up to) 46-week extension, two-way flex-dose study [Org 3770 (n=29) and amitriptyline (n=35), inpatients with major depression; Org 3770 dose range (20-60 mg/d) and amitriptyline dose range (75-225 mg/d).
Study No.: 88013 SDGRR No.: 3755	Double-blind, multicenter, (up to) 18-week extension, two-way flex-dose study [Org 3770 (n=6) and amitriptyline (n=11), elderly (age: 60-85) outpatients with major depression; Org 3770 dose range (15-45 mg/d) and amitriptyline dose range (30-90 mg/d).

APPENDIX 5.1.1 TABLE SUMMARY OF ALL STUDIES (CONTINUED)

Phase II-III

Efficacy and Safety Studies

Uncontrolled Studies

Short-Term Studies:	
Study No.: 003-001 SDGRR No.: 3513	Open-label, single-center, 4-week flex-dose study, inpatients with depression (n=12); Org 3770 dose range (5-35 mg/d).
Study No.: 22508 SDGRR No.: 3434	Open-label, 7-day, rising fixed-dose efficacy and safety study, inpatients with depression (n=15); Org 3770 dose (5 mg/d x 2 days, 10 mg/d x 2 days, 15 mg/d x 3 days).
Study No.: 80037 SDGRR No.: 1701	Single-blind, 4-week, single center, dose finding study, inpatients with depression; Org 3770 dose range [3 (n=3), 10 (n=2), 15 (n=1), 20 (n=2), and 30 mg/d (n=1)] fixed-dose: Week 1, followed by flex-dosing: Weeks 2-4).
Study No.: 81025 SDGRR No.: 3429	Single-blind, 1-6 week, single-center, dose-finding study, inpatients with depression (n=6); Org 3770 dose range (3-12 mg/d).
Study No.: 81068 SDGRR No.: 3430	Single-blind, 3-42 days, single center, flex-dose study, inpatients with depression (n=4); Org 3770 dose range (5-10 mg/d).
Study No.: 81069 SDGRR No.: 3431	Single-blind, 2-week, single center, flex-dose study, female inpatient with depression (n=1); Org 3770 dose (5 mg/d).
Study No.: 85002 SDGRR No.: 2675	Double-blind, 6-week, multicenter, fixed dose study, inpatients with major depression (n=approx. 62 in each of the 4 treatment groups); Org 3770 dose [5 (n=60), 10 (n=59), 20 (n=66), and 40 (n=62) mg/d].
Long-Term Studies:	
Study No.: None SDGRR No.: 3773	Open-label, single center, flex dose, compassionate use trial with a duration of 13-22 months, outpatients with depression (n=2); Org 3770 dose range (30-60 mg/d).
Study No.: 86005 SDGRR No.: 2506	Open-label, single center, 76 weeks (1 year and 24-week extension) 52-week, flex dose study, outpatients with depression (n=30); Org 3770 dose range (20-60 mg/d).
Study No.: 003-010 SDGRR No.: 3564	Open-label, multicenter, 76 weeks (1 year and 24-week extension), flex-dose study, outpatients with depression (n=743); Org 3770 dose range (7.5-60 mg/d).
Study No.: 003-500 SDGRR No.: 3577	Open-label, single center, flex dose, compassionate use trial with duration of 104 weeks, male patient with depression (n=1); Org 3770 dose range (5-35 mg/d).

APPENDIX 5.1.1 TABLE SUMMARY OF ALL STUDIES (CONTINUED)

Phase II-III Anxiety Studies

Study No.: 80035 SDGRR No.: 3364	Randomized, double-blind, active-(diazepam) and placebo-controlled, single center, single dose, study which included female patients who were hospitalized for gynecological surgery and assumed to have anticipatory anxiety prior to surgery (n=50 in each of the 5 treatment groups); Org 3770 dose (5, 15, and 30 mg), diazepam (10 mg), and placebo.
Study No.: 80036 SDGRR No.: 1491	Single-blind, 4-week, single center, flex-dose finding study; inpatients (n=5) and outpatients (n=5) with anxiety; Org 3770 dose range (5-30 mg/d).
Study No.: 81011 SDGRR No.: 2003	Double-blind, placebo-controlled, 4-week, rising-dose efficacy study, outpatients with anxiety (n=20 in each of two treatment groups); Org 3770 dose range (15-25 mg/d) and placebo dose range (3-4 tabs/d).

Phase II-III On-Going Study

Study No.: 86017 SDGRR No.: 3738	Randomized, double-blind, single center, 4-week, two-way flex-dose study (Org 3770 and imipramine), inpatients with depression (n=84 total); Org 3770 dose range (20-100 mg/d) and imipramine dose range (75-300 mg/d). This study is ongoing and the data are not included in the database.
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APPENDIX 5.1.2.1
DEMOGRAPHICS: ALL U.S. STUDIES (PHASE II-III)

Treatment Group	Org 3770 (N=1299)	Placebo (N=361)	Amitriptyline (N=252)	Trazodone (N=49)
Age (years) Mean $\pm$ SD Range	43 $\pm$ 13 18 - 88	45 $\pm$ 13 18 - 85	43 $\pm$ 12 18 - 93	61 $\pm$ 7 55 - 81
Weight (lbs) ^a Mean $\pm$ SD Range	(N = 1292) 165 $\pm$ 39 90 - 385	(N = 350) 166 $\pm$ 39 89 - 328	(N = 245) 168 $\pm$ 41 90 - 335	165 $\pm$ 40 105 - 268
Height (in) ^b Mean $\pm$ SD Range	(N = 1296) 67 $\pm$ 4 54 - 80	67 $\pm$ 4 53 - 76	67 $\pm$ 4 54 - 78	67 $\pm$ 5 59 - 78
Male (%) Female (%)	528 (41) 771 (59)	143 (40) 218 (60)	115 (46) 137 (54)	20 (41) 29 (59)
Caucasian (%) Non Caucasian (%)	1226 (94) 73 (6)	338 (94) 23 (6)	240 (95) 12 (5)	47 (96) 2 (4)

APPENDIX 5.1.2.2
DEMOGRAPHICS: ALL U.S. AND NON-U.S. STUDIES (PHASE II-III)

Treatment Group	Org 3770 (N = 2796)	Placebo (N = 605)	Amitriptyline (N = 666)	Trazodone (N = 149)	Clomipramine (N = 87)	Diazepam (N = 97)	Doxepin (N = 80)	Maprotiline (N = 82)
Age (yrs)	(N = 2781)							
Mean $\pm$ SD	45 $\pm$ 13	43 $\pm$ 13	48 $\pm$ 14	51 $\pm$ 13	49 $\pm$ 13	45 $\pm$ 13	41 $\pm$ 12	48 $\pm$ 11
Range	18 - 88	16 - 85	18 - 93	19 - 81	21 - 74	20 - 70	18 - 64	22 - 66
Weight (lbs)	(N = 2527)	(N = 524)	(N = 610)					
Mean $\pm$ SD	157 $\pm$ 36	161 $\pm$ 36	153 $\pm$ 36	152 $\pm$ 33	143 $\pm$ 31		148 $\pm$ 25	152 $\pm$ 28
Range	77 - 385	89 - 328	86 - 335	90 - 268	88 - 231		106 - 220	93 - 225
Height (in)	(N = 2674)		(N = 561)					
Mean $\pm$ SD	66 $\pm$ 4	66 $\pm$ 4	66 $\pm$ 4	66 $\pm$ 4	64 $\pm$ 3	65 $\pm$ 3	66 $\pm$ 3	65 $\pm$ 4
Range	54 - 80	53 - 76	54 - 78	59 - 78	56 - 72	57 - 74	59 - 76	57 - 73
Male (%)	980 (35)	221 (37)	204 (31)	49 (33)	23 (26)	14 (14)	25 (31)	22 (27)
Female (%)	1816 (65)	384 (63)	462 (69)	100 (67)	64 (74)	83 (86)	55 (69)	60 (73)

APPENDIX 5.1.3.1
DURATION OF EXPOSURE BY MODAL DOSE:
ALL U.S. and NON-U.S. STUDIES
PHASE II-III

Modal Dose (mg)	Duration of Exposure									Total (%)
	Days		Weeks					Years		
	1	2-7	1-4	4-8	8-16	16-28	28-52	1-2	>2	
Org 3770										
≤ 7.5	20	38	46	91	10	11	14	5	0	235 (9.7)
9 - 19	4	52	97	174	25	38	14	12	1	417 (17.2)
20 - 45	0	23	166	565	84	110	99	100	8	1155 (47.7)
> 45	0	0	38	376	40	39	68	55	1	617 (25.5)
Total (%)	24 (1)	113 (4.7)	347 (14)	1206 (49.8)	159 (6.6)	198 (8.2)	195 (8.0)	172 (7.1)	10 (0.4)	2424
Amitriptyline										
25 - 50	9	9	28	38	5	2	6	2	1	100
60 - 90	3	10	24	69	10	18	3	7	0	144
100 - 130	0	2	15	67	3	8	7	7	3	112
140 - 150	0	2	20	122	1	4	8	4	0	161
160 - 280	0	0	4	31	13	17	18	15	0	98
Total	12	23	91	327	32	49	42	35	4	615
Clomipramine										
50 - 100	0	0	2	23	n/a	n/a	n/a	n/a	n/a	25
125 - 200	0	0	6	27	n/a	n/a	n/a	n/a	n/a	33
Total	0	0	8	50	n/a	n/a	n/a	n/a	n/a	58

APPENDIX 5.13.1 (Continued)
DURATION OF EXPOSURE BY MODAL DOSE:
ALL U.S. and NON-U.S. STUDIES
PHASE II-III

Modal Dose (mg)	Duration of Exposure									Total
	Days		Weeks					Years		
	1	2-7	1-4	4-8	8-16	16-28	28-52	1-2	> 2	
Doxepin										
≤ 100	1	4	4	13	n/a	n/a	n/a	n/a	n/a	22
150 - 200	0	0	6	28	n/a	n/a	n/a	n/a	n/a	34
250 - 300	0	0	0	24	n/a	n/a	n/a	n/a	n/a	24
Total	1	4	10	65	n/a	n/a	n/a	n/a	n/a	80
Maprotiline										
50 - 100	0	1	1	13	n/a	n/a	n/a	n/a	n/a	15
125 - 150	0	0	1	45	n/a	n/a	n/a	n/a	n/a	46
175 - 200	0	0	0	14	n/a	n/a	n/a	n/a	n/a	14
Total	0	1	2	72	n/a	n/a	n/a	n/a	n/a	75
Trazodone										
80 - 200	1	4	11	30	n/a	n/a	n/a	n/a	n/a	46
240 - 300	0	0	3	18	n/a	n/a	n/a	n/a	n/a	21
350 - 400	0	0	2	16	n/a	n/a	n/a	n/a	n/a	18
450	0	0	8	56	n/a	n/a	n/a	n/a	n/a	64
Total	1	4	24	120	n/a	n/a	n/a	n/a	n/a	149

APPENDIX 5.1.3.2
DURATION OF EXPOSURE IN PATIENT YEARS: U.S. AND NON-U.S. STUDIES
PHASE II-III

		Org 3770	Placebo	Amitriptyline	Trazodone	Clomipramin e	Doxepin e	Maprotilin e	All Active Controls
Short-Term U.S. Controlled Studies	N	453	361	193	49				242
	Patient Years	41.7	33.4	18.5	4.6				23.1
All U.S. Controlled Studies	N	580	361	252	49				301
	Patient Years	166.5	59.8	99.6	4.6				104.2
U.S. ST UnControlled Study	N	12							
	Patient Years	0.9							
U.S. LT UnControlled Study	N	743							
	Patient Years	379.1							
All U.S. Studies	N	1299	361	252	49				301
	Patient Years	546.5	59.8	99.6	4.6				104.2
Non-U.S. Controlled Studies	N	837	133	363	100	58	80	75	676
	Patient Years	97.9	11.6	58.9	10.1	6.0	7.8	8.2	91
Non-U.S. UnControlled Studies	N	279							
	Patient Years	26.5							
Non-U.S. Other Studies	N	16							
	Patient Years	0.8							
All Non-U.S. Studies	N	1126	133	363	100	58	80	75	676
	Patient Years	125.2	11.6	58.9	10.1	6.0	7.8	8.2	91
Total	N	2425	494	615	149	58	80	75	977
	Patient Years	671.7	71.4	158.5	14.7	6.0	7.8	8.2	195.2

Based only on studies with dosing/exposure data. Long term, defined by sponsor as a study with > 6 weeks duration.

APPENDIX 5.1.3.3
DURATION OF EXPOSURE BY MEAN DOSE:
ALL U.S. and NON U.S. STUDIES

Mean Dose (mg)	Duration of Exposure									
	Days		Weeks					Years		Total (%)
	1	2-7	1-4	4-8	8-16	16-28	28-52	1-2	>2	
Org 3770										
≤ 7.5	20(1)	38(2)	34(1)	85(4)	5(<1)	3(<1)	2(<1)	0	0	187(8)
>7.5-20	4(<1)	71(3)	144(6)	270(11)	42(2)	51(2)	29(1)	18(1)	1(<1)	630(26)
>20-45	0	4(<1)	149(6)	643(27)	82(3)	106(4)	95(4)	96(4)	8(<1)	1183(49)
>45	0	0	20(1)	208(9)	30(1)	38(2)	69(3)	58(2)	1(<1)	424(17)
Total	24(1)	113(5)	347(14)	1206(50)	159(7)	198(8)	195(8)	172(7)	10(<1)	2424(100)
Amisriptyline										
≤50	9(1)	8(1)	21(3)	23(4)	3(<1)	2(<1)	2(<1)	2(<1)	0	70(11)
>50-80	3(<1)	11(2)	19(3)	64(10)	6(1)	8(1)	2(<1)	3(<1)	0	116(19)
>80-150	0	4(1)	47(8)	211(34)	10(2)	22(4)	20(3)	16(3)	4(1)	334(54)
>150	0	0	4(1)	29(5)	13(2)	17(3)	18(3)	14(2)	0	95 (15)
Total	12(2)	23(4)	91(15)	327(53)	32(5)	49(8)	42(7)	35(6)	4(1)	615(100)
Clomipramine										
≤100	0	0	4(7)	23(40)	n/a	n/a	n/a	n/a	n/a	27(47)
>100	0	0	4(7)	27(47)	n/a	n/a	n/a	n/a	n/a	31(53)
Total	0	0	8(14)	50(86)	n/a	n/a	n/a	n/a	n/a	58(100)

APPENDIX 5.1.3.3 (continued)

Mean Dose (mg)	Duration of Exposure									
	Days		Weeks					Years		Total
	1	2-7	1-4	4-8	8-16	16-28	28-52	1-2	> 2	
Doxepin										
≤ 100	1(1)	4(5)	2(2)	9(11)	n/a	n/a	n/a	n/a	n/a	16(20)
> 100-200	0	0	8(10)	46(58)	n/a	n/a	n/a	n/a	n/a	54(68)
> 200	0	0	0	10(12)	n/a	n/a	n/a	n/a	n/a	10(12)
Total	1(1)	4(5)	10(12)	65(81)	n/a	n/a	n/a	n/a	n/a	80(100)
Maprotiline										
≤100	0	1(1)	1(1)	13(17)	n/a	n/a	n/a	n/a	n/a	15(20)
> 100-150	0	0	1(1)	49(65)	n/a	n/a	n/a	n/a	n/a	50(67)
> 150	0	0	0	10(13)	n/a	n/a	n/a	n/a	n/a	10(13)
Total	0	1(1)	2(3)	72(96)	n/a	n/a	n/a	n/a	n/a	75(100)
Trazodone										
≤120	1(1)	3(2)	4(3)	5(3)	n/a	n/a	n/a	n/a	n/a	13(9)
> 120-200	0	1(1)	8(5)	28(19)	n/a	n/a	n/a	n/a	n/a	37(25)
> 200-300	0	0	7(5)	15(10)	n/a	n/a	n/a	n/a	n/a	22(15)
> 300	0	0	5(3)	72(48)	n/a	n/a	n/a	n/a	n/a	77(52)
Total	1(1)	4(3)	24(16)	120(80)	n/a	n/a	n/a	n/a	n/a	149 (100)

APPENDIX 5.1.3.4
DURATION OF EXPOSURE BY MAXIMUM DOSE:
ALL U.S. and NON U.S. STUDIES

Maximum Dose (mg)	Duration of Exposure									
	Days		Weeks					Years		Total (%)
	1	2-7	1-4	4-8	8-16	16-28	28-52	1-2	>2	
Org 3770										
≤ 7.5	20(1)	28(1)	25(1)	75(3)	3(<1)	0	2(<1)	0	0	153(6)
>7.5-20	4(<1)	81(3)	108(4)	233(10)	27(1)	37(2)	16(1)	5(<1)	0	511(21)
>20-45	0	4(<1)	163(7)	464(19)	79(3)	101(4)	85(4)	81(3)	9(<1)	986(41)
>45	0	0	51(2)	434(18)	50(2)	60(2)	92(4)	86(4)	1(<1)	774(32)
Total	24(1)	113(5)	347(14)	1206(50)	159(7)	198(8)	195(8)	172(7)	10(<1)	2424(100)
Amitriptyline										
≤50	9(1)	6(1)	11(2)	3(<1)	0	0	1(<1)	0	0	30(5)
>50-80	3(<1)	13(2)	25(4)	43(7)	3(<1)	4(1)	3(<1)	3(<1)	0	97(16)
>80-150	0	4(1)	41(7)	214(35)	10(2)	15(2)	9(1)	9(1)	1(<1)	303(49)
>150	0	0	14(2)	67(11)	19(3)	30(5)	29(5)	23(4)	3(<1)	185(30)
Total	12(2)	23(4)	91(15)	327(53)	32(5)	49(8)	42(7)	35(6)	4(1)	615(100)
Clomipramine										
≤100	0	0	1(2)	17(29)	n/a	n/a	n/a	n/a	n/a	18(31)
>100	0	0	7(12)	33(57)	n/a	n/a	n/a	n/a	n/a	40(69)
Total	0	0	8(14)	50(86)	n/a	n/a	n/a	n/a	n/a	58(100)

APPENDIX 5.1.3.4 (continued)
DURATION OF EXPOSURE BY MAXIMUM DOSE:
ALL U.S. and NON-U.S. STUDIES

Maximum Dose (mg)	Duration of Exposure									Total (%)
	Days		Weeks					Years		
	1	2-7	1-4	4-8	8-16	16-28	28-52	1-2	> 2	
Doxepin										
≤ 100	1(1)	4(5)	1(1)	8(10)	n/a	n/a	n/a	n/a	n/a	14(18)
>100-200	0	0	8(10)	32(40)	n/a	n/a	n/a	n/a	n/a	40(50)
>200	0	0	1(1)	25(31)	n/a	n/a	n/a	n/a	n/a	26(32)
Total	1(1)	4(5)	10(12)	65(81)	n/a	n/a	n/a	n/a	n/a	80(100)
Maprotiline										
≤100	0	1(1)	1(1)	12(16)	n/a	n/a	n/a	n/a	n/a	14(19)
>100-150	0	0	1(1)	45(61)	n/a	n/a	n/a	n/a	n/a	47(63)
>150	0	0	0	14(19)	n/a	n/a	n/a	n/a	n/a	14(19)
Total	0	1(1)	2(3)	72(96)	n/a	n/a	n/a	n/a	n/a	75(100)
Trazodone										
≤120	1(1)	3(2)	2(1)	3(2)	n/a	n/a	n/a	n/a	n/a	9(6)
>120-200	0	1(1)	3(2)	7(5)	n/a	n/a	n/a	n/a	n/a	11(7)
>200-300	0	0	7(5)	30(20)	n/a	n/a	n/a	n/a	n/a	37(25)
>300-400	0	0	4(3)	14(9)	n/a	n/a	n/a	n/a	n/a	18(12)
>400	0	0	8(5)	66(44)	n/a	n/a	n/a	n/a	n/a	74(50)
Total	1(1)	4(3)	24(16)	120 (81)	n/a	n/a	n/a	n/a	n/a	149(100)

**APPENDIX 7.2.1.3.1
U.S. STUDY 003-002
DEMOGRAPHIC CHARACTERISTICS**

Treatment Group	N	Age (Years)		Sex [(N%)]		Race [(N%)]	
		Mean	Range	Male	Female	White	Non-White
Org 3770	44	39	19-57	20 (45%)	24 (55%)	43 (98%)	1 (2%)
Placebo	44	40	24-61	23 (52%)	21 (48%)	39 (89%)	5 (11%)

**APPENDIX 7.2.1.3.2
U.S. STUDY 003-002
BASELINE SEVERITY OF ILLNESS**

Treatment Group	N	HAM D-21	N	HAM Item 1	N	MADRS	N	CGI (Severity)
Org 3770	44	24.2	44	2.93	44	27.9	44	4.27
Placebo	44	24.7	44	2.80	44	29.8	44	4.16

**APPENDIX 7.2.1.3.3
U.S. STUDY 003-002
DOSING INFORMATION FOR PATIENTS WHO COMPLETED**

		Week 1		Week 2		Week 3		Week 4		Week 5		Week 6	
Treatment Group	N	Mean	STD	Mean	STD	Mean	STD	Mean	STD	Mean	STD	Mean	STD
Org 3770	28	9.7	1.24	13.7	5.23	17.8	9.25	17.8	9.58	19.4	10.42	20.7	10.48

N = Number of patients who completed; intervals were calculated based on intent-to-treat efficacy visit dates. Mean dose between visits for a patient was computed as the number of capsules taken from day of previous visit until day before current visit, divided by number of days since previous visit.

APPENDIX 7.2.13.4
U.S. STUDY 003-002
SUMMARY OF EFFICACY RESULTS

	Results ^a of Observed Case Analysis For Each Visit						
Efficacy Parameter	1	2	3	4	5	6	LOCF ENDPOINT
HAM D-21 <u>Qtr 377Q vs. Plac</u>							
Rank Sum	+	+	+	+	0	0	+
One Way	+	+	+	+	0	0	+
HAM D-1 <u>Qtr 377Q vs. Plac</u>							
Rank Sum	+	+	+	+	0	0	+
One Way	+	+	+	+	0	0	+
MADRS <u>Qtr 377Q vs. Plac</u>							
Rank Sum	+	+	+	+	0	0	+
One Way	+	+	+	+	0	0	+
CGI <u>Qtr 377Q vs. Plac</u>							
Rank Sum	+	+	+	+	0	0	+
One Way	+	+	+	+	0	0	+

- ^a A statistically significant difference ($p \leq .05$) between the active drug and placebo is indicated by a +.
The absence of a statistically significant difference between the active drug and placebo is indicated by a 0.

APPENDIX 7.2.1.3.5
U.S. STUDY 003-002
MEAN CHANGE FROM BASELINE IN TOTAL HAM-D 21
INTENT-TO-TREAT GROUP
OBSERVED CASE ANALYSIS

	Baseline		Week 1		Week 2		Week 3		Week 4		Week 5		Week 6		LOCF ENDPOINT	
Treatment Group	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean
Org 3770	44	24.2	42	-5.3	42	-10.1	37	-10.9	36	-11.5	33	-13.3	26	-14.5	44	-11.7
Placebo	44	24.7	42	-2.3	37	-4.2	34	-4.9	32	-5.8	22	-10.1	19	-11.4	44	-5.4

At baseline: N = number of patients with postbaseline data and mean = mean value of the variable.
Postbaseline: N = number of patients with postbaseline data at a visit, mean = mean change from baseline.

TWO-SIDED p-VALUES FOR PAIRWISE COMPARISONS

	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	LOCF ENDPOINT
Org 3770 Versus Placebo p-Values							
Wilcoxon Rank Sum Analysis p-Value	0.044	0.001	0.002	0.007	0.229	0.301	<0.001
One-Way ANOVA p-Value	0.006	<0.001	0.001	0.009	0.196	0.286	0.001

APPENDIX 7.2.1.3.6
U.S. STUDY 003-002
MEAN CHANGE FROM BASELINE IN HAM-D 21
ITEM #1 (MOOD): INTENT-TO-TREAT GROUP
OBSERVED CASE ANALYSIS

	Baseline		Week 1		Week 2		Week 3		Week 4		Week 5		Week 6		LOCF ENDPOINT	
Treatment Group	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean
Org 3770	44	2.93	42	-0.64	42	-1.21	37	-1.35	36	-1.53	33	-1.61	26	-1.92	44	-1.50
Placebo	44	2.80	42	-0.17	37	-0.38	34	-0.53	31	-0.72	22	-1.23	19	-1.42	44	-0.61

At baseline: N = number of patients with postbaseline data and mean = mean value of the variable.
Postbaseline: N = number of patients with postbaseline data at a visit, mean = mean change from baseline.

TWO-SIDED p-VALUES FOR PAIRWISE COMPARISONS

	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	LOCF ENDPOINT
Org 3770 Versus Placebo p-Values							
Wilcoxon Rank Sum Analysis p-Value	0.008	0.001	0.001	0.005	0.297	0.188	0.002
One-Way ANOVA p-Value	0.002	<0.001	0.001	0.004	0.235	0.161	<0.001

**APPENDIX 7.2.1.3.7
U.S. STUDY 003-002
MEAN CHANGE FROM BASELINE IN MADRS
INTENT-TO-TREAT GROUP
OBSERVED CASE ANALYSIS**

Treatment Group	Baseline		Week 1		Week 2		Week 3		Week 4		Week 5		Week 6		LOCF ENDPOINT	
	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean
Org 3770	44	27.9	42	-6.0	42	-11.1	37	-11.7	36	-12.6	33	-14.6	26	-15.0	44	-12.8
Placebo	44	29.8	42	-1.4	37	-4.1	34	-5.8	32	-7.0	22	-10.8	19	-13.0	44	-6.9

At baseline: N = number of patients with postbaseline data and mean = mean value of the variable.

Postbaseline: N = number of patients with postbaseline data at a visit, mean = mean change from baseline.

TWO-SIDED p-VALUES FOR PAIRWISE COMPARISONS

	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	LOCF ENDPOINT
Org 3770 Versus Placebo p-Values							
Wilcoxon Rank Sum Analysis p-Value	<0.001	<0.001	<0.001	0.008	0.177	0.490	0.007
One-Way ANOVA p-Value	<0.001	<0.001	0.004	0.028	0.217	0.577	0.011

**APPENDIX 7.2.1.3.8
U.S. STUDY 003-002
MEAN CHANGE FROM BASELINE IN SEVERITY OF ILLNESS
INTENT-TO-TREAT GROUP
OBSERVED CASE ANALYSIS**

Treatment Group	Baseline		Week 1		Week 2		Week 3		Week 4		Week 5		Week 6		LOCF ENDPOINT	
	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean
Org 3770	44	4.27	42	-0.33	42	-0.83	37	-0.95	36	-1.17	33	-1.30	26	-1.50	44	-1.18
Placebo	44	4.16	42	0.00	37	-0.14	34	-0.18	32	-0.50	22	-0.91	19	-1.16	44	-0.45

At baseline: N = number of patients with postbaseline data and mean = mean value of the variable.

Postbaseline: N = number of patients with postbaseline data at a visit, mean = mean change from baseline.

TWO-SIDED p-VALUES FOR PAIRWISE COMPARISONS

	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	LOCF ENDPOINT
Org 3770 Versus Placebo p-Values							
Wilcoxon Rank Sum Analysis p-Value	0.002	<0.001	<0.001	0.008	0.189	0.428	0.004
One-Way ANOVA p-Value	0.002	<0.001	0.001	0.016	0.327	0.383	0.005

APPENDIX 7.2.2.3.1
U.S. STUDY 003-003
DEMOGRAPHIC CHARACTERISTICS

Treatment Group	N	Age (Years)		Sex [(N%)]		Race [(N%)]	
		Mean	Range	Male	Female	White	Non-White
Org 3770	45	43	24-65	24 (53%)	21 (47%)	44 (98%)	1 (2%)
Placebo	45	43	19-62	15 (33%)	30 (67%)	42 (93%)	3 (7%)

APPENDIX 7.2.2.3.2
U.S. STUDY 003-003
BASELINE SEVERITY OF ILLNESS

Treatment Group	N	HAM D-21	N	HAM Item 1	N	MADRS	N	CGI (Severity)
Org 3770	45	25.4	45	2.87	45	28.5	45	4.31
Placebo	45	25.5	45	2.82	44	28.8	45	4.31

APPENDIX 7.2.2.3.3
U.S. STUDY 003-003
DOSING INFORMATION FOR PATIENTS WHO COMPLETED

		Week 1		Week 2		Week 3		Week 4		Week 5		Week 6	
Treatment Group	N	Mean	STD	Mean	STD	Mean	STD	Mean	STD	Mean	STD	Mean	STD
Org 3770	28	9.9	0.41	16.1	3.27	21.9	7.06	24.5	7.72	25.8	8.04	26.6	8.14

N = Number of patients who completed; intervals were calculated based on intent-to-treat efficacy visit dates. Mean dose between visits for a patient was computed as the number of capsules taken from day of previous visit until day before current visit, divided by number of days since previous visit.

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APPENDIX 7.2.2.3.4
U.S. STUDY 003-003
SUMMARY OF EFFICACY RESULTS

	Results ^a of Observed Case Analysis For Each Visit						
Efficacy Parameter	1	2	3	4	5	6	LOCF ENDPOINT
HAM D-21 <u>Orr 3770 vs. Plac</u>							
Rank Sum	0	0	0	0	0	0	0
One Way	0	0	0	0	0	0	0
HAM D-1 <u>Orr 3770 vs. Plac</u>							
Rank Sum	0	0	0	0	0	0	0
One Way	0	0	0	0	0	0	0
MADRS <u>Orr 3770 vs. Plac</u>							
Rank Sum	0	0	0	0	0	0	0
One Way	0	0	0	+	0	0	0
CGI <u>Orr 3770 vs. Plac</u>							
Rank Sum	0	0	0	0	0	0	0
One Way	0	0	0	0	0	0	0

- ^a A statistically significant difference ($p \leq .05$) between the active drug and placebo is indicated by a +.
The absence of a statistically significant difference between the active drug and placebo is indicated by a 0.

APPENDIX 7.2.2.3.5
U.S. STUDY 003-003
MEAN CHANGE FROM BASELINE IN TOTAL HAM-D 21
INTENT-TO-TREAT GROUP
OBSERVED CASE ANALYSIS

Treatment Group	Baseline		Week 1		Week 2		Week 3		Week 4		Week 5		Week 6		LOCF ENDPOINT	
	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean
Org 3770	45	25.4	44	-3.6	36	-6.4	34	-10.0	34	-12.4	31	-11.9	27	-14.0	45	-10.4
Placebo	45	25.5	44	-2.9	42	-5.6	37	-8.5	35	-9.5	30	-11.5	24	-11.5	45	-8.8

At baseline: N = number of patients with postbaseline data and mean = mean value of the variable.

Postbaseline: N = number of patients with postbaseline data at a visit, mean = mean change from baseline.

TWO-SIDED p-VALUES FOR PAIRWISE COMPARISONS

	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	LOCF ENDPOINT
Org 3770 Versus Placebo p-Values							
Wilcoxon Rank Sum Analysis p-Value	0.147	0.733	0.321	0.143	0.914	0.508	0.490
One-Way ANOVA p-Value	0.439	0.595	0.351	0.117	0.829	0.258	0.383

APPENDIX 7.2.2.3.6
U.S. STUDY 003-003
MEAN CHANGE FROM BASELINE IN HAM-D 21
ITEM #1 (MOOD): INTENT-TO-TREAT GROUP
OBSERVED CASE ANALYSIS

Treatment Group	Baseline		Week 1		Week 2		Week 3		Week 4		Week 5		Week 6		LOCF ENDPOINT	
	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean
Org 3770	45	2.87	44	-0.43	36	-0.72	34	-0.94	34	-1.26	31	-1.13	27	-1.33	45	-1.07
Placebo	45	2.82	44	-0.34	42	-0.60	37	-0.92	35	-1.00	30	-1.30	24	-1.21	45	-0.96

At baseline: N = number of patients with postbaseline data and mean = mean value of the variable.

Postbaseline: N = number of patients with postbaseline data at a visit, mean = mean change from baseline.

TWO-SIDED p-VALUES FOR PAIRWISE COMPARISONS

	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	LOCF ENDPOINT
Org 3770 Versus Placebo p-Values							
Wilcoxon Rank Sum Analysis p-Value	0.256	0.206	0.689	0.187	0.515	0.709	0.552
One-Way ANOVA p-Value	0.477	0.490	0.915	0.260	0.536	0.667	0.609

APPENDIX 7.2.2.3.7
U.S. STUDY 003-003
MEAN CHANGE FROM BASELINE IN MADRS
INTENT-TO-TREAT GROUP
OBSERVED CASE ANALYSIS

	Baseline		Week 1		Week 2		Week 3		Week 4		Week 5		Week 6		LOCF ENDPOINT	
	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean
Org 3770	45	28.5	44	-3.2	36	-6.6	34	-9.4	34	-12.8	31	-11.8	27	-14.0	45	-10.3
Placebo	44	28.8	43	-2.0	41	-4.9	36	-7.1	34	-8.5	29	-11.0	23	-10.9	44	-7.8

At baseline: N = number of patients with postbaseline data and mean = mean value of the variable.
Postbaseline: N = number of patients with postbaseline data at a visit, mean = mean change from baseline.

TWO-SIDED p-VALUES FOR PAIRWISE COMPARISONS

	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	LOCF ENDPOINT
Org 3770 Versus Placebo p-Values							
Wilcoxon Rank Sum Analysis p-Value	0.082	0.357	0.271	0.076	0.859	0.355	0.240
One-Way ANOVA p-Value	0.222	0.257	0.245	0.047	0.733	0.253	0.217

APPENDIX 7.2.2.3.8
U.S. STUDY 003-003
MEAN CHANGE FROM BASELINE IN SEVERITY OF ILLNESS
INTENT-TO-TREAT GROUP
OBSERVED CASE ANALYSIS

	Baseline		Week 1		Week 2		Week 3		Week 4		Week 5		Week 6		LOCF ENDPOINT	
	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean
Org 3770	45	4.31	44	-0.18	36	-0.53	34	-0.79	35	-1.17	30	-1.20	27	-1.41	45	-1.09
Placebo	45	4.31	44	-0.18	42	-0.55	37	-0.81	35	-1.06	30	-1.27	24	-1.29	45	-0.98

At baseline: N = number of patients with postbaseline data and mean = mean value of the variable.
Postbaseline: N = number of patients with postbaseline data at a visit, mean = mean change from baseline.

TWO-SIDED p-VALUES FOR PAIRWISE COMPARISONS

	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	LOCF ENDPOINT
Org 3770 Versus Placebo p-Values							
Wilcoxon Rank Sum Analysis p-Value	0.641	0.771	0.961	0.470	0.728	0.754	0.713
One-Way ANOVA p-Value	1.000	0.908	0.940	0.631	0.791	0.700	0.623

APPENDIX 7.2.3.3.1
U.S. STUDY 003-008
NUMBER AND PERCENT OF PATIENTS DISCONTINUING TREATMENT BY
REASON AND WEEK

Reason for Termination	Week 1					Week 2				
	Treatment Group									
	Plac	Org 3770 5 mg	Org 3770 15 mg	Org 3770 30 mg	Org 3770 60 mg	Plac	Org 3770 5 mg	Org 3770 15 mg	Org 3770 30 mg	Org 3770 60 mg
	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)
Lack of Efficacy						1/28 (3.6)		2/30 (6.7)	2/28 (7.1)	1/30 (3.3)
Adverse Event	1/30 (3.3)	1/30 (3.3)		1/30 (3.3)			1/29 (3.4)	5/30 (16.7)	4/28 (14.3)	5/30 (16.7)
Lost-to-Follow-Up	1/30 (3.3)			1/30 (3.3)						2/30 (6.7)

APPENDIX 7.2.3.3.1 (Cont.)
U.S. STUDY 003-008
NUMBER AND PERCENT OF PATIENTS DISCONTINUING TREATMENT BY
REASON AND WEEK

Reason for Termination	Week 3					Week 4				
	Treatment Group									
	Plac	Org 3770 5 mg	Org 3770 15 mg	Org 3770 30 mg	Org 3770 60 mg	Plac	Org 3770 5 mg	Org 3770 15 mg	Org 3770 30 mg	Org 3770 60 mg
	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)
Lack of Efficacy		1/28 (3.6)			1/22 (4.5)	1/26 (3.8)	4/25 (16.0)			
Adverse Event	1/27 (3.7)	2/28 (7.1)		1/22 (4.5)	3/22 (13.6)	1/26 (3.8)	1/25 (4.0)	1/23 (4.3)		1/16 (6.3)
Non-Drug-Related				1/22 (4.5)	2/22 (9.1)	1/26 (3.8)			1/20 (5.0)	1/16 (6.3)

Patients who "discontinue treatment" in an interval are those patients whose last efficacy visit occurred in the previous interval.

% is percentage of all patients in a treatment group who did not discontinue in an earlier interval.

APPENDIX 7.2.3.3.1 (Cont.)
U.S. STUDY 003-002
NUMBER AND PERCENT OF PATIENTS DISCONTINUING TREATMENT BY
REASON AND WEEK

Reason for Termination	Week 5					Week 6				
	Treatment Group									
	Plac	Org 3770 5 mg	Org 3770 15 mg	Org 3770 30 mg	Org 3770 60 mg	Plac	Org 3770 5 mg	Org 3770 15 mg	Org 3770 30 mg	Org 3770 60 mg
	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)
Lack of Efficacy	1/23 (4.3)	1/20 (5.0)	2/22 (9.1)	3/19 (15.8)	1/14 (7.1)	2/20 (10.0)	3/18 (16.7)	2/19 (10.5)		
Adverse Event	1/23 (4.3)	1/20 (5.0)	1/22 (4.5)	1/19 (5.3)	2/14 (14.2)			2/19 (10.6)	3/15 (20.0)	2/11 (18.2)
Patient Improvement										1/11 (9.1)
Lost-to-Follow-Up	1/23 (4.3)									1/11 (9.1)

Patients who "discontinue treatment" in an interval are those patients whose last efficacy visit occurred in the previous interval.

% is percentage of all patients in a treatment group who did not discontinue in an earlier interval.

**APPENDIX 7.2.3.3.2
U.S. STUDY 003-008
DEMOGRAPHIC CHARACTERISTICS**

Treatment Group	N	Age (Years)		Sex [(N%)]		Race [(N%)]	
		Mean	Range	Male	Female	White	Non-White
Org 3770 5 mg	29	43	20-70	11 (38%)	18 (62%)	26 (90%)	3 (10%)
Org 3770 15 mg	30	38	20-57	11 (37%)	19 (63%)	24 (80%)	6 (20%)
Org 3770 30 mg	28	40	19-63	8 (29%)	20 (71%)	26 (93%)	2 (7%)
Org 3770 60 mg	30	41	25-69	9 (30%)	21 (70%)	26 (87%)	4 (13%)
Placebo	28	39	20-62	11 (39%)	17 (61%)	24 (86%)	4 (14%)

**APPENDIX 7.2.3.3.3
U.S. STUDY 003-008
BASELINE SEVERITY OF ILLNESS**

Treatment Group	N	HAM D-21	N	HAM Item 1	N	MADRS	N	CGI (Severity)
Placebo	28	25.8	28	2.86	28	27.6	28	4.32
Org 3770 5 mg	29	25.0	29	2.83	29	27.0	29	4.21
Org 3770 15 mg	30	26.0	30	2.97	30	28.2	30	4.33
Org 3770 30 mg	28	25.5	28	2.89	28	27.3	28	4.29
Org 3770 60 mg	30	25.3	30	2.87	30	27.9	30	4.23

**APPENDIX 7.2.3.3.4
U.S. STUDY 003-008
DOSING INFORMATION FOR PATIENTS WHO COMPLETED**

		Week 1		Week 2		Week 3		Week 4		Week 5		Week 6	
Treatment Group	N	Mean	STD	Mean	STD	Mean	STD	Mean	STD	Mean	STD	Mean	STD
Org 3770 5 mg	15	5.0	0.00	5.0	0.00	5.0	0.00	5.0	0.00	5.0	0.00	5.0	0.00
Org 3770 15 mg	14	10.8	0.44	15.0	0.00	15.0	0.00	15.0	0.00	15.0	0.00	15.0	0.00
Org 3770 30 mg	12	12.7	1.12	29.7	0.87	30.0	0.00	30.0	0.00	30.0	0.00	30.0	0.00
Org 3770 60 mg	7	12.9	1.77	38.8	3.97	59.4	0.98	60.0	0.00	60.0	0.00	60.0	0.00

N = Number of patients who completed; intervals were calculated based on intent-to-treat efficacy visit dates. Mean dose between visits for a patient was computed as the number of capsules taken from day of previous visit until day before current visit, divided by number of days since previous visit.

APPENDIX 7.2.3.3.5
STUDY 003-008
SUMMARY OF EFFICACY RESULTS FOR HAM D-21 AND HAM D ITEM #1

	Results ^a of Observed Case Analysis for Each Visit						
Efficacy Parameter	1	2	3	4	5	6	LOCF ENDPOINT
HAM D-21							
<u>Org 3770 5 mg vs. Plac</u>							
Rank Sum	+	0	0	0	0	0	0
One Way	+	0	0	0	0	0	0
<u>Org 3770 15 mg vs. Plac</u>							
Rank Sum	0	0	0	0	0	0	0
One Way	0	0	0	0	0	0	0
<u>Org 3770 30 mg vs. Plac</u>							
Rank Sum	+	0	0	0	0	0	0
One Way	+	0	0	0	0	0	0
<u>Org 3770 60 mg vs. Plac</u>							
Rank Sum	0	0	0	0	0	0	0
One Way	0	0	0	0	0	0	0
HAM D-1							
<u>Org 3770 5 mg vs. Plac</u>							
Rank Sum	0	0	0	0	0	0	0
One Way	0	0	0	0	0	0	0
<u>Org 3770 15 mg vs. Plac</u>							
Rank Sum	0	0	0	0	0	0	0
One Way	0	0	0	0	0	0	0
<u>Org 3770 30 mg vs. Plac</u>							
Rank Sum	0	0	0	0	0	0	0
One Way	0	0	0	0	0	0	0
<u>Org 3770 60 mg vs. Plac</u>							
Rank Sum	0	0	0	0	0	0	0
One Way	0	0	0	0	0	0	0

^a A statistically significant difference ($p \leq .05$) between the active drug and placebo is indicated by a +.
The absence of a statistically significant difference between the active drug and placebo is indicated by a 0.

APPENDIX 7.2.3.3.6
STUDY 003-008
SUMMARY OF EFFICACY RESULTS FOR CGI AND MADRS

Efficacy Parameter	Results ^a of Observed Case Analysis for Each Visit						LOCF ENDPOINT
	1	2	3	4	5	6	
MADRS							
<u>Ort 3770 5 mg vs. Plac</u>							
Rank Sum	0	0	0	0	0	0	0
One Way	0	0	0	0	0	0	0
<u>Ort 3770 15 mg vs. Plac</u>							
Rank Sum	0	0	0	0	0	0	0
One Way	0	0	0	0	0	0	0
<u>Ort 3770 30 mg vs. Plac</u>							
Rank Sum	0	0	0	0	0	0	0
One Way	0	0	0	0	0	0	0
<u>Ort 3770 60 mg vs. Plac</u>							
Rank Sum	0	0	0	0	0	0	0
One Way	0	0	0	0	0	0	0
CGI							
<u>Ort 3770 5 mg vs. Plac</u>							
Rank Sum	0	0	0	0	0	0	0
One Way	0	0	0	0	0	0	0
<u>Ort 3770 15 mg vs. Plac</u>							
Rank Sum	+	0	0	0	0	0	0
One Way	+	0	0	0	0	0	0
<u>Ort 3770 30 mg vs. Plac</u>							
Rank Sum	+	0	0	0	0	0	0
One Way	+	0	0	0	0	0	0
<u>Ort 3770 60 mg vs. Plac</u>							
Rank Sum	0	0	0	0	0	0	0
One Way	0	0	0	0	0	0	0

- ^a A statistically significant difference ($p \leq .05$) between the active drug and placebo is indicated by a +.
The absence of a statistically significant difference between the active drug and placebo is indicated by a 0.

APPENDIX 7.2.3.3.7
U.S. STUDY 003-008
MEAN CHANGE FROM BASELINE IN TOTAL HAM-D 21
INTENT-TO-TREAT GROUP
OBSERVED CASE ANALYSIS

Treatment Group	Baseline		Week 1		Week 2		Week 3		Week 4		Week 5		Week 6		LOCF ENDPOINT	
	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean
Placebo	28	25.8	28	-1.6	27	-5.6	25	-7.4	22	-8.9	20	-10.2	17	-11.4	28	-9.6
Org 3770 5mg	29	25.0	29	-3.8	27	-6.8	25	-7.8	20	-8.8	18	-8.7	15	-10.5	29	-6.8
Org 3770 15mg	30	26.0	30	-2.6	23	-5.1	23	-7.7	22	-9.1	19	-10.8	12	-13.3	30	-7.6
Org 3770 30mg	28	25.5	28	-4.0	22	-7.8	20	-9.5	19	-9.7	14	-11.9	11	-11.9	28	-7.3
Org 3770 60mg	30	25.3	30	-3.5	22	-8.5	16	-11.8	14	-11.5	11	-13.4	7	-16.6	30	-8.1

At baseline: N = number of patients with postbaseline data and mean = mean value of the variable.

Postbaseline: N = number of patients with postbaseline data at a visit, mean = mean change from baseline.

TWO-SIDED p-VALUES FOR PAIRWISE COMPARISONS

	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	LOCF ENDPOINT
Org 3770 5mg Versus Placebo p-Values							
Wilcoxon Rank Sum Analysis p-Value	0.014	0.405	0.786	0.920	0.629	0.762	0.155
One-Way ANOVA p-Value	0.025	0.386	0.822	0.956	0.546	0.736	0.174
Org 3770 15mg vs. Placebo p-Values							
Wilcoxon Rank Sum Analysis p-Value	0.110	0.899	0.836	0.879	0.822	0.579	0.253
One-Way ANOVA p-Value	0.193	0.763	0.858	0.907	0.781	0.507	0.318
Org 3770 30mg vs. Placebo p-Values							
Wilcoxon Rank Sum Analysis p-Value	0.015	0.119	0.212	0.656	0.482	0.621	0.282
One-Way ANOVA p-Value	0.016	0.132	0.252	0.682	0.519	0.873	0.278
Org 3770 60mg vs. Placebo p-Values							
Wilcoxon Rank Sum Analysis p-Value	0.074	0.100	0.028	0.298	0.408	0.252	0.346
One-Way ANOVA p-Value	0.065	0.066	0.028	0.265	0.267	0.155	0.458

APPENDIX 7.2.3.3.8
U.S. STUDY 003-008
MEAN CHANGE FROM BASELINE IN HAM-D 21
ITEM #1 (MOOD): INTENT-TO-TREAT GROUP
OBSERVED CASE ANALYSIS

Treatment Group	Baseline		Week 1		Week 2		Week 3		Week 4		Week 5		Week 6		LOCF ENDPOINT	
	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean
Placebo	28	2.86	28	-0.25	27	-0.44	25	-0.64	22	-0.91	20	-1.00	17	-1.24	28	-0.89
Org 3770 5mg	29	2.83	29	-0.28	27	-0.56	25	-0.68	20	-0.85	18	-0.83	15	-0.93	29	-0.59
Org 3770 15mg	30	2.97	30	-0.23	25	-0.57	23	-0.78	22	-1.00	19	-1.16	12	-1.33	30	-0.53
Org 3770 30mg	28	2.89	28	-0.29	22	-0.82	20	-1.10	19	-1.05	14	-1.21	11	-1.27	28	-0.71
Org 3770 60mg	30	2.87	30	-0.13	22	-0.73	16	-1.06	14	-0.79	11	-1.18	7	-1.57	30	-0.67

At baseline: N = number of patients with postbaseline data and mean = mean value of the variable.
Postbaseline: N = number of patients with postbaseline data at a visit, mean = mean change from baseline.

TWO-SIDED p-VALUES FOR PAIRWISE COMPARISONS

	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	LOCF ENDPOINT
Org 3770 5mg Versus Placebo p-Values							
Wilcoxon Rank Sum Analysis p-Value	0.786	0.368	0.786	0.968	0.590	0.440	0.323
One-Way ANOVA p-Value	0.842	0.561	0.857	0.827	0.581	0.367	0.200
Org 3770 15mg vs. Placebo p-Values							
Wilcoxon Rank Sum Analysis p-Value	0.892	0.477	0.541	0.785	0.658	0.781	0.901
One-Way ANOVA p-Value	0.885	0.553	0.528	0.746	0.602	0.792	0.813
Org 3770 30mg vs. Placebo p-Values							
Wilcoxon Rank Sum Analysis p-Value	0.773	0.099	0.130	0.670	0.583	0.922	0.475
One-Way ANOVA p-Value	0.768	0.098	0.090	0.630	0.545	0.925	0.492
Org 3770 60mg vs. Placebo p-Values							
Wilcoxon Rank Sum Analysis p-Value	0.266	0.083	0.088	0.798	0.618	0.402	0.446
One-Way ANOVA p-Value	0.265	0.148	0.092	0.704	0.610	0.449	0.363

APPENDIX 7.2.3.3.9
U.S. STUDY 003-008
MEAN CHANGE FROM BASELINE IN MADRS
INTENT-TO-TREAT GROUP
OBSERVED CASE ANALYSIS

Treatment Group	Baseline		Week 1		Week 2		Week 3		Week 4		Week 5		Week 6		LOCF ENDPOINT	
	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean
Placebo	28	27.6	28	-1.8	27	-5.0	25	-7.2	22	-8.9	20	-10.3	17	-10.4	28	-8.3
Org 3770 5mg	29	27.0	28	-3.4	27	-6.4	25	-7.4	20	-8.3	18	-8.7	15	-9.9	29	-6.2
Org 3770 15mg	30	28.2	30	-2.7	23	-5.3	23	-7.7	22	-8.6	19	-9.9	12	-13.5	30	-7.2
Org 3770 30mg	28	27.3	28	-3.3	22	-7.0	20	-9.0	19	-9.0	14	-11.2	11	-10.5	28	-6.7
Org 3770 60mg	30	27.9	30	-3.6	22	-8.0	16	-12.0	14	-10.3	11	-12.1	7	-13.8	30	-7.3

At baseline: N = number of patients with postbaseline data and mean = mean value of the variable.
Postbaseline: N = number of patients with postbaseline data at a visit, mean = mean change from baseline.

TWO-SIDED p-VALUES FOR PAIRWISE COMPARISONS

	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	LOCF ENDPOINT
Org 3770 5mg Versus Placebo p-Values							
Wilcoxon Rank Sum Analysis p-Value	0.112	0.425	0.985	0.772	0.568	0.955	0.288
One-Way ANOVA p-Value	0.116	0.423	0.917	0.753	0.514	0.883	0.303
Org 3770 15mg vs. Placebo p-Values							
Wilcoxon Rank Sum Analysis p-Value	0.260	0.853	0.869	0.672	0.989	0.318	0.436
One-Way ANOVA p-Value	0.287	0.862	0.813	0.884	0.897	0.342	0.637
Org 3770 30mg vs. Placebo p-Values							
Wilcoxon Rank Sum Analysis p-Value	0.074	0.333	0.403	0.937	0.766	0.850	0.337
One-Way ANOVA p-Value	0.130	0.293	0.390	0.967	0.756	0.951	0.473
Org 3770 60mg vs. Placebo p-Values							
Wilcoxon Rank Sum Analysis p-Value	0.200	0.062	0.049	0.795	0.577	0.356	0.570
One-Way ANOVA p-Value	0.120	0.086	0.031	0.561	0.576	0.376	0.653

APPENDIX 7.2.3.3.10
U.S. STUDY 003-008
MEAN CHANGE FROM BASELINE IN SEVERITY OF ILLNESS
INTENT-TO-TREAT GROUP
OBSERVED CASE ANALYSIS

Treatment Group	Baseline		Week 1		Week 2		Week 3		Week 4		Week 5		Week 6		LOCF ENDPOINT	
	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean
Placebo	28	4.32	28	0.04	27	-0.41	25	-0.68	22	-1.09	20	-1.10	17	-1.47	28	-1.11
Org 3770 5mg	29	4.21	29	-0.17	27	-0.52	25	-0.76	20	-0.90	18	-1.06	15	-1.33	29	-0.76
Org 3770 15mg	30	4.33	30	-0.20	23	-0.48	23	-0.78	22	-0.95	19	-1.21	12	-1.67	30	-0.77
Org 3770 30mg	28	4.29	28	-0.25	22	-0.55	20	-1.00	19	-0.95	15	-1.60	11	-1.73	28	-0.86
Org 3770 60mg	30	4.23	30	-0.20	22	-0.77	16	-1.19	14	-1.07	11	-1.45	7	-2.14	30	-0.90

At baseline: N = number of patients with postbaseline data and mean = mean value of the variable.
Postbaseline: N = number of patients with postbaseline data at a visit, mean = mean change from baseline.

TWO-SIDED p-VALUES FOR PAIRWISE COMPARISONS

	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	LOCF ENDPOINT
Org 3770 5mg Versus Placebo p-Values							
Wilcoxon Rank Sum Analysis p-Value	0.088	0.651	0.808	0.764	0.901	0.937	0.237
One-Way ANOVA p-Value	0.086	0.526	0.738	0.548	0.898	0.738	0.221
Org 3770 15mg vs. Placebo p-Values							
Wilcoxon Rank Sum Analysis p-Value	0.041	0.793	0.677	0.757	0.589	0.447	0.164
One-Way ANOVA p-Value	0.036	0.687	0.669	0.683	0.770	0.651	0.277
Org 3770 30mg vs. Placebo p-Values							
Wilcoxon Rank Sum Analysis p-Value	0.034	0.616	0.262	0.774	0.358	0.530	0.265
One-Way ANOVA p-Value	0.029	0.465	0.233	0.690	0.258	0.608	0.446
Org 3770 60mg vs. Placebo p-Values							
Wilcoxon Rank Sum Analysis p-Value	0.088	0.112	0.088	0.787	0.345	0.179	0.464
One-Way ANOVA p-Value	0.076	0.072	0.078	0.960	0.419	0.249	0.505

**APPENDIX 7.2.4.3.1
U.S. STUDY 003-020
DEMOGRAPHIC CHARACTERISTICS**

Treatment Group	N	Age (Years)		Sex [(N%)]		Race [(N%)]	
		Mean	Range	Male	Female	White	Non-White
Amitriptyline	40	43	20-78	22 (55%)	18 (45%)	39 (98%)	1 (3%)
Org 3770	41	44	24-69	22 (54%)	19 (46%)	41 (100%)	
Placebo	39	45	21-85	15 (38%)	24 (62%)	37 (95%)	2 (5%)

**APPENDIX 7.2.4.3.2
U.S. STUDY 003-020
BASELINE SEVERITY OF ILLNESS**

Treatment Group	N	HAM D-21	N	HAM Item 1	N	MADRS	N	CGI (Severity)
Org 3770	41	27.8	41	2.68	41	25.8	41	4.46
Amitriptyline	40	29.2	40	2.83	40	27.8	40	4.73
Placebo	39	29.5	39	2.92	39	28.8	39	4.77

**APPENDIX 7.2.4.3.3
U.S. STUDY 003-020
DOSING INFORMATION FOR PATIENTS WHO COMPLETED**

		Week 1		Week 2		Week 3		Week 4		Week 5		Week 6	
Treatment Group	N	Mean	STD	Mean	STD	Mean	STD	Mean	STD	Mean	STD	Mean	STD
Amitriptyline	26	52.0	18.66	84.9	40.88	126.0	68.38	145.0	71.90	140.9	75.77	137.1	75.12
Org 3770	25	6.4	2.16	10.6	3.26	14.8	4.78	18.0	7.08	21.0	7.90	23.5	9.11

N = Number of patients who completed; intervals were calculated based on intent-to-treat efficacy visit dates.
Mean dose between visits for a patient was computed as the number of capsules taken from day of previous visit until day before current visit, divided by number of days since previous visit.

APPENDIX 7.2.4.3.4
U.S. STUDY 003-020
SUMMARY OF EFFICACY RESULTS

	Results ^a of Observed Case Analysis by Visit						
Efficacy Parameter	1	2	3	4	5	6	LOCF ENDPOINT
HAM D-21 <u>Qtr 3770 vs. Plac</u>							
Rank Sum	0	0	+	+	0	+	+
One Way	0	0	+	+	0	+	+
Ami vs. Plac							
Rank Sum	0	+	+	+	0	+	+
One Way	0	+	+	+	0	+	+
HAM D-1 <u>Qtr 3770 vs. Plac</u>							
Rank Sum	0	0	0	0	0	+	+
One Way	0	0	0	0	0	+	+
Ami vs. Plac							
Rank Sum	0	0	0	0	0	+	+
One Way	0	0	0	0	0	+	+
MADRS <u>Qtr 3770 vs. Plac</u>							
Rank Sum	0	0	0	0	0	0	+
One Way	0	0	0	+	0	+	+
Ami vs. Plac							
Rank Sum	0	+	+	+	0	+	+
One Way	0	+	+	+	0	+	+
CGI <u>Qtr 3770 vs. Plac</u>							
Rank Sum	0	0	+	+	0	+	+
One Way	0	0	+	+	0	+	+
Ami vs. Plac							
Rank Sum	0	+	+	+	+	+	+
One Way	0	+	+	+	+	+	+

- ^a A statistically significant difference ($p \leq .05$) between the active drug and placebo is indicated by a +.
The absence of a statistically significant difference between the active drug and placebo is indicated by a 0.

APPENDIX 7.2.4.3.5
U.S. STUDY 003-020
MEAN CHANGE FROM BASELINE IN TOTAL HAM-D 21
INTENT-TO-TREAT GROUP
OBSERVED CASE ANALYSIS

Treatment Group	Baseline		Week 1		Week 2		Week 3		Week 4		Week 5		Week 6		LOCF ENDPOINT	
	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean
Org 3770	41	27.8	39	-3.3	36	-5.8	33	-8.7	28	-9.9	25	-10.8	23	-13.0	41	-10.3
Placebo	39	29.5	37	-3.0	35	-4.0	32	-4.7	30	-5.5	28	-8.7	24	-6.2	39	-4.8
Amitriptyline	40	29.2	38	-3.4	38	-7.4	32	-8.6	32	-10.7	26	-12.8	25	-14.4	40	-11.5

At baseline: N = number of patients with postbaseline data and mean = mean value of the variable.
Postbaseline: N = number of patients with postbaseline data at a visit, mean = mean change from baseline.

TWO-SIDED p-VALUES FOR PAIRWISE COMPARISONS

	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	LOCF ENDPOINT
Org 3770 Versus Placebo p-Values							
Wilcoxon Rank Sum Analysis p-Value	0.691	0.069	0.019	0.011	0.257	0.007	0.006
One-Way ANOVA p-Value	0.764	0.155	0.025	0.010	0.296	0.005	0.002
Amitriptyline vs. Placebo p-Values							
Wilcoxon Rank Sum Analysis p-Value	0.377	0.003	0.023	0.004	0.051	0.002	<0.001
One-Way ANOVA p-Value	0.715	0.010	0.022	0.004	0.069	<0.001	<0.001

APPENDIX 7.2.4.3.6
U.S. STUDY 003-020
MEAN CHANGE FROM BASELINE IN HAM-D 21
ITEM #1 (MOOD): INTENT-TO-TREAT GROUP
OBSERVED CASE ANALYSIS

Treatment Group	Baseline		Week 1		Week 2		Week 3		Week 4		Week 5		Week 6		LOCF ENDPOINT	
	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean
Org 3770	41	2.68	39	-0.10	36	-0.53	33	-0.67	28	-0.75	25	-0.92	23	-1.35	41	-1.10
Placebo	39	2.92	37	-0.22	35	-0.37	32	-0.50	30	-0.73	28	-0.96	24	-0.71	39	-0.54
Amitriptyline	40	2.83	38	-0.24	38	-0.66	32	-0.75	32	-1.16	26	-1.27	25	-1.48	40	-1.18

At baseline: N = number of patients with postbaseline data and mean = mean value of the variable.
Postbaseline: N = number of patients with postbaseline data at a visit, mean = mean change from baseline.

TWO-SIDED p-VALUES FOR PAIRWISE COMPARISONS

	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	LOCF ENDPOINT
Org 3770 Versus Placebo p-Values							
Wilcoxon Rank Sum Analysis p-Value	0.615	0.339	0.310	0.980	0.946	0.012	0.008
One-Way ANOVA p-Value	0.422	0.397	0.398	0.938	0.858	0.008	0.003
Amitriptyline vs. Placebo p-Values							
Wilcoxon Rank Sum Analysis p-Value	0.675	0.110	0.273	0.165	0.285	0.027	0.017
One-Way ANOVA p-Value	0.892	0.128	0.240	0.096	0.259	0.013	0.004

APPENDIX 7.2.4.3.7
U.S. STUDY 003-020
MEAN CHANGE FROM BASELINE IN MADRS
INTENT-TO-TREAT GROUP
OBSERVED CASE ANALYSIS

Treatment Group	Baseline		Week 1		Week 2		Week 3		Week 4		Week 5		Week 6		LOCF ENDPOINT	
	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean
Org 3770	41	25.8	39	-2.1	36	-4.0	33	-6.8	28	-9.2	25	-9.8	23	-12.6	41	-9.4
Placebo	39	28.8	37	-2.4	35	-3.1	32	-3.7	30	-5.1	28	-8.4	24	-6.7	39	-4.5
Amitriptyline	40	27.8	38	-2.4	38	-6.5	32	-8.3	32	-11.1	26	-12.6	25	-14.2	40	-11.6

At baseline: N = number of patients with postbaseline data and mean = mean value of the variable.
Postbaseline: N = number of patients with postbaseline data at a visit, mean = mean change from baseline.

TWO-SIDED p-VALUES FOR PAIRWISE COMPARISONS

	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	LOCF ENDPOINT
Org 3770 Versus Placebo p-Values							
Wilcoxon Rank Sum Analysis p-Value	0.810	0.324	0.178	0.052	0.396	0.054	0.027
One-Way ANOVA p-Value	0.856	0.548	0.140	0.041	0.517	0.023	0.015
Amitriptyline vs. Placebo p-Values							
Wilcoxon Rank Sum Analysis p-Value	0.794	0.031	0.019	0.004	0.082	0.019	0.006
One-Way ANOVA p-Value	0.942	0.031	0.017	0.004	0.092	0.008	0.001

APPENDIX 7.2.4.3.8
U.S. STUDY 003-020
MEAN CHANGE FROM BASELINE IN SEVERITY OF ILLNESS
INTENT-TO-TREAT GROUP
OBSERVED CASE ANALYSIS

Treatment Group	Baseline		Week 1		Week 2		Week 3		Week 4		Week 5		Week 6		LOCF ENDPOINT	
	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean
Org 3770	41	4.46	39	-0.28	36	-0.56	33	-0.94	28	-1.32	25	-1.36	23	-1.83	41	-1.46
Placebo	39	4.77	37	-0.22	35	-0.34	32	-0.44	30	-0.60	28	-0.89	24	-0.83	39	-0.59
Amitriptyline	40	4.73	38	-0.29	38	-0.87	32	-0.97	32	-1.41	26	-1.73	25	-2.20	40	-1.65

At baseline: N = number of patients with postbaseline data and mean = mean value of the variable.
Postbaseline: N = number of patients with postbaseline data at a visit, mean = mean change from baseline.

TWO-SIDED p-VALUES FOR PAIRWISE COMPARISONS

	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	LOCF ENDPOINT
Org 3770 Versus Placebo p-Values							
Wilcoxon Rank Sum Analysis p-Value	0.454	0.155	0.004	0.004	0.084	0.006	0.001
One-Way ANOVA p-Value	0.643	0.211	0.010	0.010	0.131	0.004	<0.001
Amitriptyline vs. Placebo p-Values							
Wilcoxon Rank Sum Analysis p-Value	0.424	0.008	0.002	0.002	0.012	<0.001	<0.001
One-Way ANOVA p-Value	0.597	0.007	0.003	0.003	0.013	<0.001	<0.001

Appendix 7.2.5.3.1
U.S. STUDY 003-021
DEMOGRAPHIC CHARACTERISTICS

Treatment Group	N	Age (Years)		Sex [(N%)]		Race [(N%)]	
		Mean	Range	Male	Female	White	Non-White
Amitriptyline	48	44	18-74	22 (46%)	26 (54%)	42 (88%)	6 (13%)
Org 3770	45	45	23-66	20 (44%)	25 (56%)	42 (93%)	3 (7%)
Placebo	48	48	24-76	21 (44%)	27 (56%)	40 (83%)	8 (17%)

Appendix 7.2.5.3.2
U.S. STUDY 003-021
BASELINE SEVERITY OF ILLNESS

Treatment Group	N	HAM D-21	N	HAM Item 1	N	MADRS	N	CGI (Severity)
Org 3770	45	24.2	45	2.33	45	29.1	45	4.07
Amitriptyline	48	25.0	48	2.54	48	29.7	48	4.19
Placebo	48	24.4	48	2.27	48	30.4	48	4.04

Appendix 7.2.5.3.3
U.S. STUDY 003-021
DOSING INFORMATION FOR PATIENTS WHO COMPLETED

		Week 1		Week 2		Week 3		Week 4		Week 5		Week 6	
Treatment Group	N	Mean	STD	Mean	STD	Mean	STD	Mean	STD	Mean	STD	Mean	STD
Amitriptyline	32	56.1	13.73	101.5	36.68	119.8	51.86	117.8	55.19	126.8	60.87	116.0	63.57
Org 3770	25	7.6	0.96	14.8	4.24	18.7	7.04	20.7	7.76	23.5	8.01	20.5	9.58

N = Number of patients who completed; intervals were calculated based on intent-to-treat efficacy visit dates. Mean dose between visits for a patient was computed as the number of capsules taken from day of previous visit until day before current visit, divided by number of days since previous visit.

Appendix 7.2.5.3.4
U.S. STUDY 003-021
SUMMARY OF EFFICACY RESULTS

Efficacy Parameter	Results ^a of Observed Case Analysis by Visit						LOCF ENDPOINT
	1	2	3	4	5	6	
HAM D-21 <u>Qrx 3770 vs. Plac</u>							
Rank Sum	+	+	0	0	0	0	0
One Way	+	+	0	0	0	+	0
Ami vs. Plac							
Rank Sum	+	+	0	+	0	0	+
One Way	+	+	0	+	0	0	+
HAM D-1 <u>Qrx 3770 vs. Plac</u>							
Rank Sum	0	0	0	0	0	0	0
One Way	0	0	0	0	0	+	0
Ami vs. Plac							
Rank Sum	+	+	+	+	0	0	+
One Way	+	+	+	+	+	0	+
MADRS <u>Qrx 3770 vs. Plac</u>							
Rank Sum	+	0	0	0	0	+	0
One Way	+	0	0	0	0	+	0
Ami vs. Plac							
Rank Sum	+	0	0	+	0	0	+
One Way	+	0	0	+	0	0	+
CGI <u>Qrx 3770 vs. Plac</u>							
Rank Sum	0	0	0	0	0	0	0
One Way	0	0	0	0	0	0	0
Ami vs. Plac							
Rank Sum	+	0	0	+	0	0	+
One Way	+	0	0	+	0	0	+

- ^a A statistically significant difference ($p \leq .05$) between the active drug and placebo is indicated by a +.
The absence of a statistically significant difference between the active drug and placebo is indicated by a 0.

Appendix 7.2.5.3.5
U.S. STUDY 003-021
MEAN CHANGE FROM BASELINE IN TOTAL HAM-D 21
INTENT-TO-TREAT GROUP
OBSERVED CASE ANALYSIS

Treatment Group	Baseline		Week 1		Week 2		Week 3		Week 4		Week 5		Week 6		LOCF ENDPOINT	
	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean
Org 3770	45	24.2	43	-6.0	41	-9.5	39	-9.8	39	-12.1	26	-14.4	22	-13.8	45	-11.7
Placebo	48	24.4	48	-3.2	42	-6.3	36	-9.6	32	-9.4	23	-12.9	21	-17.4	48	-9.5
Amitriptyline	48	25.0	46	-7.2	41	-10.8	35	-12.4	37	-13.8	31	-15.0	27	-17.1	48	-13.6

At baseline: N = number of patients with postbaseline data and mean = mean value of the variable.

Postbaseline: N = number of patients with postbaseline data at a visit, mean = mean change from baseline.

TWO-SIDED p-VALUES FOR PAIRWISE COMPARISONS

	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	LOCF ENDPOINT
Org 3770 Versus Placebo p-Values							
Wilcoxon Rank Sum Analysis p-Value	0.007	0.033	0.890	0.174	0.495	0.064	0.223
One-Way ANOVA p-Value	0.010	0.036	0.868	0.133	0.451	0.044	0.210
Amitriptyline vs. Placebo p-Values							
Wilcoxon Rank Sum Analysis p-Value	0.002	<0.001	0.093	0.020	0.301	0.934	0.015
One-Way ANOVA p-Value	<0.001	<0.001	0.092	0.008	0.316	0.884	0.015

Appendix 7.2.5.3.6
U.S. STUDY 003-021
MEAN CHANGE FROM BASELINE IN HAM-D 21
ITEM #1 (MOOD): INTENT-TO-TREAT GROUP
OBSERVED CASE ANALYSIS

Treatment Group	Baseline		Week 1		Week 2		Week 3		Week 4		Week 5		Week 6		LOCF ENDPOINT	
	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean
Org 3770	45	2.33	43	-0.37	41	-0.83	39	-0.87	39	-1.05	26	-1.27	22	-1.18	45	-0.91
Placebo	48	2.27	48	-0.19	42	-0.52	36	-0.94	32	-0.81	23	-1.17	21	-1.86	48	-0.81
Amitriptyline	48	2.54	46	-0.70	41	-1.07	35	-1.46	37	-1.51	31	-1.77	27	-1.89	48	-1.50

At baseline: N = number of patients with postbaseline data and mean = mean value of the variable.

Postbaseline: N = number of patients with postbaseline data at a visit, mean = mean change from baseline.

TWO-SIDED p-VALUES FOR PAIRWISE COMPARISONS

	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	LOCF ENDPOINT
Org 3770 Versus Placebo p-Values							
Wilcoxon Rank Sum Analysis p-Value	0.153	0.159	0.841	0.265	0.820	0.061	0.634
One-Way ANOVA p-Value	0.285	0.166	0.753	0.352	0.767	0.047	0.688
Amitriptyline vs. Placebo p-Values							
Wilcoxon Rank Sum Analysis p-Value	0.006	0.011	0.016	0.006	0.065	1.000	0.005
One-Way ANOVA p-Value	0.008	0.012	0.020	0.005	0.042	0.911	0.005

Appendix 7.2.5.3.7
U.S. STUDY 003-021
MEAN CHANGE FROM BASELINE IN MADRS
INTENT-TO-TREAT GROUP
OBSERVED CASE ANALYSIS

Treatment Group	Baseline		Week 1		Week 2		Week 3		Week 4		Week 5		Week 6		LOCF ENDPOINT	
	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean
Org 3770	45	29.1	43	-6.6	41	-11.0	39	-10.8	39	-12.6	26	-16.4	22	-13.5	45	-11.7
Placebo	48	30.4	48	-3.5	42	-7.8	36	-11.5	32	-10.8	23	-14.0	21	-21.3	48	-11.3
Amitriptyline	48	29.7	46	-8.1	41	-10.0	35	-14.1	37	-17.0	31	-19.0	27	-21.2	48	-16.0

At baseline: N = number of patients with postbaseline data and mean = mean value of the variable.
Postbaseline: N = number of patients with postbaseline data at a visit, mean = mean change from baseline.

TWO-SIDED p-VALUES FOR PAIRWISE COMPARISONS

	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	LOCF ENDPOINT
Org 3770 Versus Placebo p-Values							
Wilcoxon Rank Sum Analysis p-Value	0.039	0.129	0.795	0.326	0.357	0.002	0.812
One-Way ANOVA p-Value	0.032	0.103	0.755	0.444	0.370	0.002	0.851
Amitriptyline vs. Placebo p-Values							
Wilcoxon Rank Sum Analysis p-Value	0.007	0.135	0.259	0.005	0.067	0.950	0.035
One-Way ANOVA p-Value	0.005	0.231	0.202	0.004	0.070	0.965	0.043

Appendix 7.2.5.3.8
U.S. STUDY 003-021
MEAN CHANGE FROM BASELINE IN SEVERITY OF ILLNESS
INTENT-TO-TREAT GROUP
OBSERVED CASE ANALYSIS

Treatment Group	Baseline		Week 1		Week 2		Week 3		Week 4		Week 5		Week 6		LOCF ENDPOINT	
	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean
Org 3770	45	4.07	43	-0.35	41	-0.71	39	-0.85	39	-1.05	26	-1.42	22	-1.59	45	-1.13
Placebo	48	4.04	48	-0.15	42	-0.45	36	-0.86	32	-0.75	23	-1.22	21	-2.00	48	-0.92
Amitriptyline	48	4.19	46	-0.46	41	-0.68	35	-1.11	37	-1.35	31	-1.55	27	-1.81	48	-1.40

At baseline: N = number of patients with postbaseline data and mean = mean value of the variable.
Postbaseline: N = number of patients with postbaseline data at a visit, mean = mean change from baseline.

TWO-SIDED p-VALUES FOR PAIRWISE COMPARISONS

	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	LOCF ENDPOINT
Org 3770 Versus Placebo p-Values							
Wilcoxon Rank Sum Analysis p-Value	0.073	0.238	0.806	0.174	0.441	0.178	0.237
One-Way ANOVA p-Value	0.054	0.123	0.949	0.201	0.491	0.167	0.335
Amitriptyline vs. Placebo p-Values							
Wilcoxon Rank Sum Analysis p-Value	0.019	0.144	0.157	0.005	0.285	0.473	0.019
One-Way ANOVA p-Value	0.009	0.116	0.231	0.008	0.282	0.519	0.038

Appendix 7.2.6.3.1
U.S. STUDY 003-022
DEMOGRAPHIC CHARACTERISTICS

Treatment Group	N	Age (Years)		Sex [(N%)]		Race [(N%)]	
		Mean	Range	Male	Female	White	Non-White
Amitriptyline	50	39	20-93	13 (26%)	37 (74%)	48 (96%)	2 (4%)
Org 3770	49	39	18-65	20 (41%)	29 (59%)	47 (96%)	2 (4%)
Placebo	50	37	18-67	15 (30%)	35 (70%)	49 (98%)	1 (2%)

Appendix 7.2.6.3.2
U.S. STUDY 003-022
BASELINE SEVERITY OF ILLNESS

Treatment Group	N	HAM D-21	N	HAM Item 1	N	MADRS	N	CGI (Severity)
Org 3770	49	33.0	49	3.04	49	37.7	49	5.06
Amitriptyline	50	32.0	50	2.80	50	36.8	50	5.20
Placebo	50	31.2	50	2.86	50	36.8	50	5.14

Appendix 7.2.6.3.3
U.S. STUDY 003-022
DOSING INFORMATION FOR PATIENTS WHO COMPLETED

		Week 1		Week 2		Week 3		Week 4		Week 5		Week 6	
Treatment Group	N	Mean	STD	Mean	STD	Mean	STD	Mean	STD	Mean	STD	Mean	STD
Amitriptyline	40	75.2	11.43	103.0	44.01	139.8	72.81	156.8	82.86	177.3	80.20	186.3	84.18
Org 3770	41	9.6	1.24	16.6	5.12	25.0	9.64	27.1	9.18	29.9	8.12	30.8	8.07

N = Number of patients who completed; intervals were calculated based on intent-to-treat efficacy visit dates. Mean dose between visits for a patient was computed as the number of capsules taken from day of previous visit until day before current visit, divided by number of days since previous visit.

Appendix 7.2.6.3.4
U.S. STUDY 003-022
SUMMARY OF EFFICACY RESULTS

	Results ^a of Observed Case Analysis by Visit						
Efficacy Parameter	1	2	3	4	5	6	LOCF ENDPOINT
HAM D-21 <u>Org 3770 vs. Plac</u>							
Rank Sum	+	+	+	+	+	+	+
One Way	+	+	+	+	+	+	+
<u>Ami vs. Plac</u>							
Rank Sum	+	+	+	+	+	+	+
One Way	+	+	+	+	+	+	+
HAM D-1 <u>Org 3770 vs. Plac</u>							
Rank Sum	+	+	+	+	+	+	+
One Way	+	+	+	+	+	+	+
<u>Ami vs. Plac</u>							
Rank Sum	0	+	+	0	0	0	0
One Way	0	+	+	+	0	0	0
MADRS <u>Org 3770 vs. Plac</u>							
Rank Sum	0	+	0	0	+	+	+
One Way	0	+	0	0	+	+	+
<u>Ami vs. Plac</u>							
Rank Sum	+	+	+	+	+	+	+
One Way	0	+	+	+	+	+	+
CGI <u>Org 3770 vs. Plac</u>							
Rank Sum	0	0	0	0	+	+	+
One Way	0	+	0	0	0	+	+
<u>Ami vs. Plac</u>							
Rank Sum	0	0	+	+	+	+	+
One Way	0	0	+	+	+	+	+

^a A statistically significant difference ($p \leq .05$) between the active drug and placebo is indicated by a +.
The absence of a statistically significant difference between the active drug and placebo is indicated by a 0.

Appendix 7.2.6.3.5
U.S. STUDY 003-022
MEAN CHANGE FROM BASELINE IN TOTAL HAM-D 21
INTENT-TO-TREAT GROUP
OBSERVED CASE ANALYSIS

Treatment Group	Baseline		Week 1		Week 2		Week 3		Week 4		Week 5		Week 6		LOCF ENDPOINT	
	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean
Org 3770	49	33.0	49	-3.5	47	-7.9	46	-9.7	44	-13.2	42	-16.1	37	-19.4	49	-16.1
Placebo	50	31.2	50	-2.1	48	-4.2	46	-6.7	45	-9.3	42	-10.5	36	-11.0	50	-9.0
Amitriptyline	50	32.0	50	-3.5	47	-8.0	45	-12.0	43	-14.0	40	-16.9	40	-16.8	50	-14.1

At baseline: N = number of patients with postbaseline data and mean = mean value of the variable.
Postbaseline: N = number of patients with postbaseline data at a visit, mean = mean change from baseline.

TWO-SIDED p-VALUES FOR PAIRWISE COMPARISONS

	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	LOCF ENDPOINT
Org 3770 Versus Placebo p-Values							
Wilcoxon Rank Sum Analysis p-Value	0.037	0.001	0.029	0.030	0.005	<0.001	0.001
One-Way ANOVA p-Value	0.027	<0.001	0.030	0.019	0.003	<0.001	<0.001
Amitriptyline vs. Placebo p-Value							
Wilcoxon Rank Sum Analysis p-Value	0.025	<0.001	<0.001	0.005	<0.001	0.005	0.005
One-Way ANOVA p-Value	0.026	<0.001	<0.001	0.004	<0.001	0.004	0.005

Appendix 7.2.6.3.6
U.S. STUDY 003-022
MEAN CHANGE FROM BASELINE IN HAM-D 21
ITEM #1 (MOOD): INTENT-TO-TREAT GROUP
OBSERVED CASE ANALYSIS

Treatment Group	Baseline		Week 1		Week 2		Week 3		Week 4		Week 5		Week 6		LOCF ENDPOINT	
	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean
Org 3770	49	3.04	49	-0.37	47	-0.79	46	-1.11	44	-1.55	42	-1.69	37	-1.97	49	-1.69
Placebo	50	2.86	50	-0.16	48	-0.35	46	-0.59	45	-0.93	42	-1.19	36	-1.31	50	-1.00
Amitriptyline	50	2.80	50	-0.30	47	-0.83	45	-1.11	43	-1.35	40	-1.50	40	-1.55	50	-1.38

At baseline: N = number of patients with postbaseline data and mean = mean value of the variable.
Postbaseline: N = number of patients with postbaseline data at a visit, mean = mean change from baseline.

TWO-SIDED p-VALUES FOR PAIRWISE COMPARISONS

	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	LOCF ENDPOINT
Org 3770 Versus Placebo p-Values							
Wilcoxon Rank Sum Analysis p-Value	0.033	0.003	0.001	0.011	0.030	0.022	0.009
One-Way ANOVA p-Value	0.033	0.003	0.008	0.006	0.045	0.019	0.006
Amitriptyline vs. Placebo p-Values							
Wilcoxon Rank Sum Analysis p-Value	0.099	0.002	0.002	0.063	0.178	0.349	0.091
One-Way ANOVA p-Value	0.098	0.001	0.002	0.050	0.182	0.337	0.092

Appendix 7.2.6.3.7
U.S. STUDY 003-022
MEAN CHANGE FROM BASELINE IN MADRS
INTENT-TO-TREAT GROUP
OBSERVED CASE ANALYSIS

Treatment Group	Baseline		Week 1		Week 2		Week 3		Week 4		Week 5		Week 6		LOCF ENDPOINT	
	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean
Org 3770	49	37.7	49	-4.2	47	-8.8	46	-10.7	44	-14.6	42	-18.4	37	-22.6	49	-18.7
Placebo	50	36.8	50	-2.7	48	-5.6	46	-8.5	45	-11.6	42	-13.0	36	-13.4	50	-11.0
Amitriptyline	50	36.8	50	-4.1	47	-9.8	45	-14.1	43	-16.3	40	-19.5	40	-19.4	50	-16.2

At baseline: N = number of patients with postbaseline data and mean = mean value of the variable.

Postbaseline: N = number of patients with postbaseline data at a visit, mean = mean change from baseline.

TWO-SIDED p-VALUES FOR PAIRWISE COMPARISONS

	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	LOCF ENDPOINT
Org 3770 Versus Placebo p-Values							
Wilcoxon Rank Sum Analysis p-Value	0.063	0.025	0.164	0.123	0.022	0.005	0.009
One-Way ANOVA p-Value	0.089	0.019	0.210	0.139	0.022	0.002	0.003
Amitriptyline vs. Placebo p-Values							
Wilcoxon Rank Sum Analysis p-Value	0.039	0.001	<0.001	0.015	0.005	0.023	0.030
One-Way ANOVA p-Value	0.084	<0.001	<0.001	0.021	0.005	0.022	0.027

Appendix 7.2.6.3.8
U.S. STUDY 003-022
MEAN CHANGE FROM BASELINE IN SEVERITY OF ILLNESS
INTENT-TO-TREAT GROUP
OBSERVED CASE ANALYSIS

Treatment Group	Baseline		Week 1		Week 2		Week 3		Week 4		Week 5		Week 6		LOCF ENDPOINT	
	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean
Org 3770	49	5.06	49	-0.12	47	-0.49	46	-0.72	44	-1.11	42	-1.50	37	-2.24	49	-1.82
Placebo	50	5.14	50	-0.04	48	-0.25	46	-0.50	45	-0.78	42	-1.02	36	-1.11	50	-0.84
Amitriptyline	50	5.20	50	-0.02	47	-0.45	45	-0.82	43	-1.21	40	-1.75	40	-1.80	50	-1.48

At baseline: N = number of patients with postbaseline data and mean = mean value of the variable.

Postbaseline: N = number of patients with postbaseline data at a visit, mean = mean change from baseline.

TWO-SIDED p-VALUES FOR PAIRWISE COMPARISONS

	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	LOCF ENDPOINT
Org 3770 Versus Placebo p-Values							
Wilcoxon Rank Sum Analysis p-Value	0.136	0.054	0.203	0.145	0.030	0.002	0.003
One-Way ANOVA p-Value	0.135	0.039	0.169	0.119	0.033	0.001	0.001
Amitriptyline vs. Placebo p-Values							
Wilcoxon Rank Sum Analysis p-Value	0.568	0.084	0.041	0.030	0.004	0.014	0.011
One-Way ANOVA p-Value	0.562	0.066	0.035	0.031	0.004	0.021	0.014

**Appendix 7.2.7.3.1
U.S. STUDY 003-023
DEMOGRAPHIC CHARACTERISTICS**

Treatment Group	N	Age (Years)		Sex [(N%)]		Race [(N%)]	
		Mean	Range	Male	Female	White	Non-White
Org 3770	49	63	55-80	28 (57%)	21 (43%)	49 (100%)	
Placebo	49	62	55-79	20 (41%)	29 (59%)	49 (100%)	
Trazodone	48	61	55-81	19 (40%)	29 (60%)	46 (96%)	2 (4%)

**Appendix 7.2.7.3.2
U.S. STUDY 003-023
BASELINE SEVERITY OF ILLNESS**

Treatment Group	N	HAM D-21	N	HAM Item 1	N	MADRS	N	CGI (Severity)
Org 3770	49	24.6	49	2.55	48	25.3	49	3.73
Trazodone	48	24.6	48	2.65	47	26.1	48	3.96
Placebo	49	23.5	49	2.67	49	23.9	49	3.90

**Appendix 7.2.7.3.3
U.S. STUDY 003-023
DOSING INFORMATION FOR PATIENTS WHO COMPLETED**

Treatment Group	N	Week 1		Week 2		Week 3		Week 4		Week 5		Week 6	
		Mean	STD	Mean	STD	Mean	STD	Mean	STD	Mean	STD	Mean	STD
Org 3770	40	10.0	0.23	15.5	3.88	22.2	4.91	26.2	7.37	29.1	7.49	28.7	8.47
Trazodone	34	79.2	3.32	128.5	29.46	164.6	47.08	193.7	51.04	216.8	56.17	219.5	57.41

N = Number of patients who completed; intervals were calculated based on intent-to-treat efficacy visit dates. Mean dose between visits for a patient was computed as the number of capsules taken from day of previous visit until day before current visit, divided by number of days since previous visit.

Appendix 7.2.7.3.4
U.S. STUDY 003-023
SUMMARY OF EFFICACY RESULTS

	Results ^a of Observed Case Analysis by Visit						
Efficacy Parameters	1	2	3	4	5	6	LOCF ENDPOINT
HAM D-21 <u>Qtr 3770 vs. Plac</u>							
Rank Sum	0	+	0	+	0	+	+
One Way	0	+	+	+	0	+	+
<u>Traz vs. Plac</u>							
Rank Sum	0	0	0	0	0	0	0
One Way	0	0	0	0	0	0	0
HAM D-1 <u>Qtr 3770 vs. Plac</u>							
Rank Sum	0	0	0	0	0	0	0
One Way	0	0	0	0	0	0	0
<u>Traz vs. Plac</u>							
Rank Sum	0	0	0	0	0	0	0
One Way	0	0	0	0	0	0	0
MADRS <u>Qtr 3770 vs. Plac</u>							
Rank Sum	0	+	0	0	0	0	+
One Way	0	+	0	0	0	0	+
<u>Traz vs. Plac</u>							
Rank Sum	0	+	0	0	0	0	0
One Way	0	+	+	0	0	0	0
CGI <u>Qtr 3770 vs. Plac</u>							
Rank Sum	+	0	0	0	0	0	0
One Way	+	0	0	0	0	0	0
<u>Traz vs. Plac</u>							
Rank Sum	0	0	0	0	0	0	0
One Way	0	0	0	0	0	0	0

- ^a A statistically significant difference ($p \leq .05$) between the active drug and placebo is indicated by a +.
The absence of a statistically significant difference between the active drug and placebo is indicated by a 0.

Appendix 7.2.7.3.5
U.S. STUDY 003-023
**MEAN CHANGE FROM BASELINE IN TOTAL HAM-D 21
INTENT-TO-TREAT GROUP
OBSERVED CASE ANALYSIS**

Treatment Group	Baseline		Week 1		Week 2		Week 3		Week 4		Week 5		Week 6		LOCF ENDPOINT	
	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean
Org 3770	49	24.6	49	-4.1	49	-7.1	43	-8.7	42	-10.8	39	-11.0	37	-11.1	49	-9.9
Placebo	49	23.5	48	-2.8	45	-4.2	41	-6.1	40	-6.8	37	-9.3	34	-7.6	49	-6.6
Trazodone	48	24.6	48	-3.4	44	-6.4	40	-7.1	37	-8.2	34	-9.9	32	-8.8	48	-7.8

At baseline: N = number of patients with postbaseline data and mean = mean value of the variable.
Postbaseline: N = number of patients with postbaseline data at a visit, mean = mean change from baseline.

TWO-SIDED p-VALUES FOR PAIRWISE COMPARISONS

	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	LOCF ENDPOINT
Org 3770 Versus Placebo p-Values							
Wilcoxon Rank Sum Analysis p-Value	0.152	0.007	0.058	0.007	0.330	0.049	0.019
One-Way ANOVA p-Value	0.153	0.005	0.041	0.002	0.237	0.036	0.020
Trazodone vs. Placebo p-Values							
Wilcoxon Rank Sum Analysis p-Value	0.520	0.070	0.580	0.491	0.991	0.572	0.435
One-Way ANOVA p-Value	0.502	0.060	0.457	0.346	0.768	0.491	0.412

Appendix 7.2.7.3.6
U.S. STUDY 003-023
**MEAN CHANGE FROM BASELINE IN HAM-D 21
ITEM #1 (MOOD): INTENT-TO-TREAT GROUP
OBSERVED CASE ANALYSIS**

Treatment Group	Baseline		Week 1		Week 2		Week 3		Week 4		Week 5		Week 6		LOCF ENDPOINT	
	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean
Org 3770	49	2.55	49	-0.37	49	-0.55	43	-0.86	42	-1.10	39	-1.10	37	-1.22	49	-0.96
Placebo	49	2.67	48	-0.42	45	-0.58	41	-0.83	40	-0.88	37	-1.27	34	-0.97	49	-0.84
Trazodone	48	2.65	48	-0.38	44	-0.68	40	-0.78	37	-0.97	34	-1.09	32	-0.94	48	-0.81

At baseline: N = number of patients with postbaseline data and mean = mean value of the variable.
Postbaseline: N = number of patients with postbaseline data at a visit, mean = mean change from baseline.

TWO-SIDED p-VALUES FOR PAIRWISE COMPARISONS

	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	LOCF ENDPOINT
Org 3770 Versus Placebo p-Values							
Wilcoxon Rank Sum Analysis p-Value	0.753	0.761	0.755	0.210	0.426	0.352	0.447
One-Way ANOVA p-Value	0.736	0.672	0.882	0.276	0.481	0.382	0.559
Trazodone vs. Placebo p-Values							
Wilcoxon Rank Sum Analysis p-Value	0.776	0.419	0.948	0.783	0.563	0.968	0.896
One-Way ANOVA p-Value	0.800	0.587	0.797	0.701	0.550	0.914	0.921

Appendix 7.2.7.3.7
U.S. STUDY 003-023
MEAN CHANGE FROM BASELINE IN MADRS
INTENT-TO-TREAT GROUP
OBSERVED CASE ANALYSIS

	Baseline		Week 1		Week 2		Week 3		Week 4		Week 5		Week 6		LOCF ENDPOINT	
Treatment Group	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean
Org 3770	48	25.3	48	-2.8	48	-6.2	42	-6.3	41	-8.5	38	-9.5	36	-10.4	48	-8.8
Placebo	49	22.9	48	-2.0	45	-2.3	41	-3.5	40	-6.2	37	-7.3	34	-6.8	49	-5.0
Trazodone	47	26.1	47	-2.9	43	-5.8	39	-6.9	36	-9.1	33	-10.3	31	-10.1	47	-8.1

At baseline: N = number of patients with postbaseline data and mean = mean value of the variable.
Postbaseline: N = number of patients with postbaseline data at a visit, mean = mean change from baseline.

TWO-SIDED p-VALUES FOR PAIRWISE COMPARISONS

	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	LOCF ENDPOINT
Org 3770 Versus Placebo p-Values							
Wilcoxon Rank Sum Analysis p-Value	0.538	0.008	0.171	0.374	0.423	0.138	0.024
One-Way ANOVA p-Value	0.571	0.014	0.135	0.228	0.281	0.110	0.049
Trazodone vs. Placebo p-Values							
Wilcoxon Rank Sum Analysis p-Value	0.316	0.031	0.052	0.227	0.276	0.200	0.085
One-Way ANOVA p-Value	0.503	0.037	0.043	0.183	0.182	0.160	0.103

Appendix 7.2.7.3.8
U.S. STUDY 003-023
MEAN CHANGE FROM BASELINE IN SEVERITY OF ILLNESS
INTENT-TO-TREAT GROUP
OBSERVED CASE ANALYSIS

	Baseline		Week 1		Week 2		Week 3		Week 4		Week 5		Week 6		LOCF ENDPOINT	
Treatment Group	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean
Org 3770	49	3.73	49	0.06	49	-0.31	43	-0.43	42	-0.74	39	-0.77	37	-1.03	49	-0.80
Placebo	49	3.90	48	-0.17	45	-0.29	41	-0.46	40	-0.58	37	-0.86	34	-0.82	49	-0.39
Trazodone	48	3.96	48	-0.08	44	-0.43	40	-0.40	38	-0.63	34	-0.85	32	-0.31	48	-0.67

At baseline: N = number of patients with postbaseline data and mean = mean value of the variable.
Postbaseline: N = number of patients with postbaseline data at a visit, mean = mean change from baseline.

TWO-SIDED p-VALUES FOR PAIRWISE COMPARISONS

	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	LOCF ENDPOINT
Org 3770 Versus Placebo p-Values							
Wilcoxon Rank Sum Analysis p-Value	0.036	0.805	0.741	0.426	0.470	0.518	0.361
One-Way ANOVA p-Value	0.033	0.916	0.823	0.451	0.699	0.300	0.405
Trazodone vs. Placebo p-Values							
Wilcoxon Rank Sum Analysis p-Value	0.318	0.373	0.364	0.696	0.837	0.978	0.652
One-Way ANOVA p-Value	0.424	0.367	0.730	0.818	0.961	0.970	0.744

Appendix 7.2.8.3.1
U.S. STUDY 003-024
DEMOGRAPHIC CHARACTERISTICS

Treatment Group	N	Age (Years)		Sex [(N%)]		Race [(N%)]	
		Mean	Range	Male	Female	White	Non-White
Amitriptyline	49	43	21-72	24 (49%)	25 (51%)	46 (94%)	3 (6%)
Org 3770	50	44	20-75	23 (46%)	27 (54%)	49 (98%)	1 (2%)
Placebo	48	40	19-68	16 (33%)	32 (67%)	48 (100%)	

Appendix 7.2.8.3.2
U.S. STUDY 003-024
BASELINE SEVERITY OF ILLNESS

Treatment Group	N	HAM D-21	N	HAM Item 1	N	MADRS	N	CGI (Severity)
Org 3770	50	27.5	50	2.80	50	28.7	50	4.44
Amitriptyline	49	27.6	49	2.71	49	27.9	49	4.49
Placebo	48	27.6	48	2.67	48	27.7	48	4.31

Appendix 7.2.8.3.3
U.S. STUDY 003-024
DOSING INFORMATION FOR PATIENTS WHO COMPLETED

Treatment Group	N	Week 1		Week 2		Week 3		Week 4		Week 5		Week 6	
		Mean	STD	Mean	STD	Mean	STD	Mean	STD	Mean	STD	Mean	STD
Amitriptyline	37	72.5	15.21	101.3	32.41	129.2	42.60	139.4	46.97	153.4	51.87	143.5	59.96
Org 3770	32	9.8	0.50	13.6	3.64	18.1	5.05	21.1	6.99	22.7	8.56	22.0	7.74

N = Number of patients who completed; intervals were calculated based on intent-to-treat efficacy visit dates. Mean dose between visits for a patient was computed as the number of capsules taken from day of previous visit until day before current visit, divided by number of days since previous visit.

Appendix 7.2.8.3.4
U.S. STUDY 003-024
SUMMARY OF EFFICACY RESULTS

	Results ^a of Observed Case Analysis by Visit						
Efficacy Parameters	1	2	3	4	5	6	LOCF ENDPOINT
HAM D-21 <u>Orr 3770 vs. Plac</u>							
Rank Sum	0	+	0	+	0	0	+
One Way	0	+	0	+	0	+	+
Ami vs. Plac							
Rank Sum	+	+	+	+	0	+	+
One Way	+	+	+	+	0	+	+
HAM D-1 <u>Orr 3770 vs. Plac</u>							
Rank Sum	0	0	+	+	0	0	+
One Way	0	0	+	+	0	0	+
Ami vs. Plac							
Rank Sum	0	+	+	+	0	+	+
One Way	0	+	+	+	0	+	+
MADRS <u>Orr 3770 vs. Plac</u>							
Rank Sum	0	+	+	+	0	+	+
One Way	0	+	+	+	0	+	+
Ami vs. Plac							
Rank Sum	+	+	+	+	0	+	+
One Way	+	+	+	+	0	+	+
CGI <u>Orr 3770 vs. Plac</u>							
Rank Sum	0	0	0	+	0	0	+
One Way	0	0	0	+	0	0	+
Ami vs. Plac							
Rank Sum	+	+	+	+	0	+	+
One Way	+	+	+	+	0	+	+

^a A statistically significant difference ($p \leq .05$) between the active drug and placebo is indicated by a +.
The absence of a statistically significant difference between the active drug and placebo is indicated by a 0.

Appendix 7.2.8.3.5
U.S. STUDY 003-024
MEAN CHANGE FROM BASELINE IN TOTAL HAM-D 21
INTENT-TO-TREAT GROUP
OBSERVED CASE ANALYSIS

Treatment Group	Baseline		Week 1		Week 2		Week 3		Week 4		Week 5		Week 6		LOCF ENDPOINT	
	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean
Org 3770	50	27.5	49	-5.5	48	-9.6	46	-12.3	45	-13.1	36	-15.3	30	-15.7	50	-12.1
Placebo	48	27.6	48	-3.5	46	-6.1	44	-9.2	43	-8.4	29	-13.0	27	-11.1	48	-7.7
Amitriptyline	49	27.6	48	-7.4	48	-11.6	45	-14.3	44	-14.2	39	-15.5	35	-16.0	49	-13.9

At baseline: N = number of patients with postbaseline data and mean = mean value of the variable.

Postbaseline: N = number of patients with postbaseline data at a visit, mean = mean change from baseline.

TWO-SIDED p-VALUES FOR PAIRWISE COMPARISONS

	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	LOCF ENDPOINT
Org 3770 Versus Placebo p-Values							
Wilcoxon Rank Sum Analysis p-Value	0.071	0.023	0.139	0.012	0.322	0.060	0.015
One-Way ANOVA p-Value	0.118	0.024	0.060	0.013	0.215	0.043	0.018
Amitriptyline vs. Placebo p-Values							
Wilcoxon Rank Sum Analysis p-Value	<0.001	0.001	0.007	0.002	0.297	0.031	<0.001
One-Way ANOVA p-Value	0.002	<0.001	0.001	0.001	0.179	0.035	0.002

Appendix 7.2.8.3.6
U.S. STUDY 003-024
MEAN CHANGE FROM BASELINE IN HAM-D 21
ITEM #1 (MOOD): INTENT-TO-TREAT GROUP
OBSERVED CASE ANALYSIS

Treatment Group	Baseline		Week 1		Week 2		Week 3		Week 4		Week 5		Week 6		LOCF ENDPOINT	
	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean
Org 3770	50	2.80	49	-0.53	48	-0.67	46	-1.11	45	-1.20	36	-1.50	30	-1.40	50	-1.08
Placebo	48	2.67	48	-0.25	46	-0.43	44	-0.64	43	-0.65	29	-1.03	27	-0.89	48	-0.58
Amitriptyline	49	2.71	48	-0.44	48	-0.96	45	-1.38	44	-1.18	39	-1.31	35	-1.46	49	-1.31

At baseline: N = number of patients with postbaseline data and mean = mean value of the variable.

Postbaseline: N = number of patients with postbaseline data at a visit, mean = mean change from baseline.

TWO-SIDED p-VALUES FOR PAIRWISE COMPARISONS

	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	LOCF ENDPOINT
Org 3770 Versus Placebo p-Values							
Wilcoxon Rank Sum Analysis p-Value	0.098	0.263	0.037	0.017	0.068	0.075	0.020
One-Way ANOVA p-Value	0.078	0.219	0.034	0.022	0.069	0.084	0.033
Amitriptyline vs. Placebo p-Values							
Wilcoxon Rank Sum Analysis p-Value	0.227	0.010	0.002	0.026	0.253	0.049	0.002
One-Way ANOVA p-Value	0.177	0.006	<0.001	0.024	0.307	0.049	0.002

APPENDIX 8.7.1 (Cont.)

Summary of Serious Adverse Events Occurring in Mirtazapine-Treated Patients and Considered Unlikely to be Drug-Related

Study Number	Patient Number	Age	Dose* (mg/d)	Duration (days)	Adverse Event
Miscellaneous					
003-010	634	55	0	405	L Hip Pin Removal
	630	41	60	341	Back surgery
	419	34	45	376	Musculoskeletal Injury
	314	63	60	140	Head Trauma
	275	49	15	531	Abdominal Fistula
	156	21	30	285	Jaw Surgery
	145	36	45	393	Foot Surgery

*Dose at time of event.

Appendix 7.2.8.3.7
U.S. STUDY 003-024
MEAN CHANGE FROM BASELINE IN MADRS
INTENT-TO-TREAT GROUP
OBSERVED CASE ANALYSIS

Treatment Group	Baseline		Week 1		Week 2		Week 3		Week 4		Week 5		Week 6		LOCF ENDPOINT	
	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean
Org 3770	50	28.7	49	-5.8	48	-9.2	46	-12.2	45	-13.2	36	-15.1	30	-15.9	50	-12.4
Placebo	48	27.7	48	-3.1	46	-5.5	44	-7.6	43	-7.6	29	-13.1	27	-9.1	48	-6.2
Amitriptyline	49	27.9	48	-7.7	46	-11.1	45	-14.8	44	-14.6	39	-16.2	35	-16.8	49	-15.0

At baseline: N = number of patients with postbaseline data and mean = mean value of the variable.

Postbaseline: N = number of patients with postbaseline data at a visit, mean = mean change from baseline.

TWO-SIDED p-VALUES FOR PAIRWISE COMPARISONS

	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	LOCF ENDPOINT
Org 3770 Versus Placebo p-Values							
Wilcoxon Rank Sum Analysis p-Value	0.076	0.005	0.047	0.004	0.432	0.026	0.002
One-Way ANOVA p-Value	0.058	0.016	0.016	0.005	0.345	0.016	0.003
Amitriptyline vs. Placebo p-Value							
Wilcoxon Rank Sum Analysis p-Value	<0.001	<0.001	<0.001	<0.001	0.178	0.010	<0.001
One-Way ANOVA p-Value	<0.001	<0.001	<0.001	<0.001	0.142	0.004	<0.001

Appendix 7.2.8.3.8
U.S. STUDY 003-024
MEAN CHANGE FROM BASELINE IN SEVERITY OF ILLNESS
INTENT-TO-TREAT GROUP
OBSERVED CASE ANALYSIS

Treatment Group	Baseline		Week 1		Week 2		Week 3		Week 4		Week 5		Week 6		LOCF ENDPOINT	
	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean
Org 3770	50	4.44	49	-0.29	48	-0.83	46	-1.22	45	-1.49	36	-1.78	30	-1.87	50	-1.36
Placebo	48	4.31	48	-0.21	46	-0.48	44	-0.75	43	-0.91	29	-1.38	27	-1.22	48	-0.77
Amitriptyline	49	4.49	48	-0.60	48	-1.13	45	-1.62	44	-1.68	39	-1.77	35	-2.00	49	-1.71

At baseline: N = number of patients with postbaseline data and mean = mean value of the variable.

Postbaseline: N = number of patients with postbaseline data at a visit, mean = mean change from baseline.

TWO-SIDED p-VALUES FOR PAIRWISE COMPARISONS

	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	LOCF ENDPOINT
Org 3770 Versus Placebo p-Values							
Wilcoxon Rank Sum Analysis p-Value	0.592	0.052	0.071	0.025	0.114	0.053	0.010
One-Way ANOVA p-Value	0.568	0.106	0.053	0.036	0.221	0.097	0.037
Amitriptyline vs. Placebo p-Values							
Wilcoxon Rank Sum Analysis p-Value	0.002	<0.001	<0.001	0.007	0.192	0.028	<0.001
One-Way ANOVA p-Value	0.003	0.004	<0.001	0.006	0.263	0.044	0.001

**Appendix 7.2.9.3.1
NON-U.S. STUDY 84008
DEMOGRAPHIC CHARACTERISTICS**

Treatment Group	N	Age (Years)		Sex [(N%)]	
		Mean	Range	Male	Female
Org 4419	40	43	24-63	18 (45%)	22 (55%)
Org 4420	40	46	28-63	10 (25%)	30 (75%)
Placebo	41	43	22-61	17 (41%)	24 (59%)

**Appendix 7.2.9.3.2
NON-U.S. STUDY 84008
BASELINE SEVERITY OF ILLNESS INTENT-TO-TREAT GROUP**

Treatment Group	N	HAM D-21	N	HAM Item 1	N	MADRS	N	GAS
Org 4419	38	27.6	38	2.89	40	31.7	40	38.8
Org 4420	35	27.9	35	3.00	40	32.3	40	39.9
Placebo	39	27.9	39	3.03	41	32.7	41	38.2

**Appendix 7.2.9.3.3
NON-U.S. STUDY 84008
DOSING INFORMATION FOR PATIENTS WHO COMPLETED**

		Visit 1		Visit 2		Visit 3		Visit 4		Visit 5	
Treatment Group	N	Mean	STD	Mean	STD	Mean	STD	Mean	STD	Mean	STD
Org 4419	38	20.0	0.00	30.8	2.73	40.8	2.73	51.3	3.43	58.4	4.95
Org 4420	35	20.0	0.00	30.3	1.69	41.7	4.53	51.4	3.55	58.3	5.68

Visit 1: Days 1 - 10

Visit 2: Days 11 - 17

Visit 3: Days 18 - 24

Visit 4: Days 25 - 31

Visit 5: Days 32 - 38

N = Number of patients who completed; intervals were calculated based on intent-to-treat efficacy visit dates.

Mean dose between visits for a patient was computed as the number of capsules taken from day of previous visit until day before current visit, divided by number of days since previous visit.

Appendix 7.2.9.3.4
NON-U.S. STUDY 84008
MEAN CHANGE FROM BASELINE IN TOTAL HAM-D 21
INTENT-TO-TREAT GROUP
OBSERVED CASE ANALYSIS

Treatment Group	Baseline		Visit 3*		LOCF ENDPOINT	
	N	Mean	N	Mean	N	Mean
Placebo	39	27.9	39	-15.8	39	-15.8
Org 4419	38	27.6	38	-18.6	38	-18.6
Org 4420	35	27.9	35	-16.1	35	-16.1

- * The HAM-D 21 was only administered at Visit 3.
 At baseline: N = number of patients with postbaseline data and mean = mean value of the variable.
 Postbaseline: N = number of patients with postbaseline data at a visit, mean = mean change from baseline.

TWO-SIDED p-VALUES FOR PAIRWISE COMPARISONS

	Visit 3	LOCF ENDPOINT
Org 4419 Versus Placebo -Values		
Wilcoxon Rank Sum Analysis p-Value	0.227	.227
One-Way ANOVA p-Value	0.110	.110
Org 4420 vs. Placebo p-Values		
Wilcoxon Rank Sum Analysis p-Value	0.858	.858
One-Way ANOVA p-Value	0.889	.889

Appendix 7.2.9.3.5
NON-U.S. STUDY 84008
MEAN CHANGE FROM BASELINE IN HAM ITEM 1: MOOD
INTENT-TO-TREAT GROUP
OBSERVED CASE ANALYSIS

	Baseline		Visit 3		LOCF ENDPOINT	
Treatment Group	N	Mean	N	Mean	N	Mean
Placebo	39	3.03	39	-1.54	39	-1.54
Org 4419	38	2.89	38	-1.55	38	-1.55
Org 4420	35	3.00	35	-1.49	35	-1.49

Visit 3: Days 28 - 41

At baseline: N = number of patients with postbaseline data and mean = mean value of the variable.

Postbaseline: N = number of patients with postbaseline data at a visit, mean = mean change from baseline.

TWO-SIDED p-VALUES FOR PAIRWISE COMPARISONS

	Visit 3	LOCF ENDPOINT
Org 4419 Versus Placebo p-Values		
Wilcoxon Rank Sum Analysis p-Value	0.724	.724
One-Way ANOVA p-Value	0.938	.938
Org 4420 vs. Placebo p-Values		
Wilcoxon Rank Sum Analysis p-Value	0.584	.584
One-Way ANOVA p-Value	0.787	.787

Appendix 7.2.9.3.6
NON-U.S. STUDY 84008
MEAN CHANGE FROM BASELINE IN MADRS
INTENT-TO-TREAT GROUP
OBSERVED CASE ANALYSIS

	Baseline		Visit 1		Visit 2		Visit 3		LOCF ENDPOINT	
Treatment Group	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean
Placebo	41	32.7	41	-4.5	40	-11.6	39	-16.7	41	-16.2
Org 4419	40	31.7	40	-4.9	40	-10.6	38	-19.8	40	-18.5
Org 4420	40	32.3	40	-4.6	38	-10.4	35	-16.9	40	-15.4

Visit 1: Days 1 - 13

Visit 2: Days 14 - 27

Visit 3: Days 28 - 41

At baseline: N = number of patients with postbaseline data and mean = mean value of the variable.

Postbaseline: N = number of patients with postbaseline data at a visit, mean = mean change from baseline.

TWO-SIDED p-VALUES FOR PAIRWISE COMPARISONS

	Visit 1	Visit 2	Visit 3	LOCF ENDPOINT
Org 4419 Versus Placebo p-Values				
Wilcoxon Rank Sum Analysis p-Value	0.780	0.426	0.165	.222
One-Way ANOVA p-Value	0.645	0.513	0.101	.263
Org 4420 vs. Placebo p-Values				
Wilcoxon Rank Sum Analysis p-Value	0.656	0.212	0.867	.548
One-Way ANOVA p-Value	0.965	0.401	0.900	.670

Appendix 7.2.9.3.7
NON-U.S. STUDY 84008
MEAN CHANGE FROM BASELINE IN THE GAS
INTENT-TO-TREAT GROUP
OBSERVED CASE ANALYSIS

Treatment Group	Baseline		Visit 1		Visit 2		Visit 3		Visit 4		Visit 5		LOCF ENDPOINT	
	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean
Placebo	41	38.2	41	1.9	40	8.0	40	11.7	39	14.3	39	18.7	41	17.9
Org 4419	40	38.8	40	2.4	40	6.9	40	10.8	38	14.9	38	21.1	40	19.7
Org 4420	40	39.9	40	2.4	39	6.3	38	10.0	36	14.7	35	18.7	40	17.0

Visit 1: Days 1 - 10

Visit 2: Days 11 - 17

Visit 3: Days 18 - 24

Visit 4: Days 25 - 31

Visit 5: Days 32 - 38

At baseline: N = number of patients with postbaseline data and mean = mean value of the variable.

Postbaseline: N = number of patients with postbaseline data at a visit, mean = mean change from baseline.

TWO-SIDED p-VALUES FOR PAIRWISE COMPARISONS

	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	LOCF ENDPOINT
Org 4419 Versus Placebo p-Values						
Wilcoxon Rank Sum Analysis p-Value	0.905	0.502	0.919	0.350	0.185	0.226
One-Way ANOVA p-Value	0.553	0.382	0.556	0.700	0.247	0.422
Org 4420 vs. Placebo p-Values						
Wilcoxon Rank Sum Analysis p-Value	0.683	0.208	0.426	0.432	0.987	0.691
One-Way ANOVA p-Value	0.537	0.161	0.259	0.829	0.993	0.677

**Appendix 7.2.10.3.1
NON-U.S. STUDY 84023
DEMOGRAPHIC CHARACTERISTICS**

Treatment Group	N	Age (Years)		Sex [(N%)]	
		Mean	Range	Male	Female
Org 3770	59	46	20-83	25 (42%)	34 (58%)
Placebo	54	46	16-75	28 (52%)	26 (48%)

**Appendix 7.2.10.3.2
NON-U.S. STUDY 84023
INTENT-TO-TREAT GROUP**

Treatment Group	N ^a	HAM D-21	N ^a	HAM Item 1	N ^a	MADRS	N	GAS
Org 3770	44	25.6	44	2.89	54	32.4	58	40.9
Placebo	45	26.0	45	2.78	52	33.0	52	40.8

^a The HAM D-21 was administered at the beginning and the end of the study and the MADRS was administered at Days 0, 14, 28, and 42. Hence, more patients have endpoint MADRS data than have endpoint data for the HAM D-21.

**Appendix 7.2.10.3.3
NON-U.S. STUDY 84023
DOSING INFORMATION FOR PATIENTS WHO COMPLETED**

		Visit 1		Visit 2		Visit 3		Visit 4		Visit 5		Visit 6	
		Mean	STD	Mean	STD	Mean	STD	Mean	STD	Mean	STD	Mean	STD
Treatment Group	N												
Org 3770	37	14.9	0.71	21.6	4.70	27.1	7.66	30.9	10.60	32.2	10.86	32.9	11.43

Visit 1: Days 1 - 10

Visit 2: Days 11 - 17

Visit 3: Days 18 - 24

Visit 4: Days 25 - 31

Visit 5: Days 32 - 38

Visit 6: Days 39 - 45

N = Number of patients who completed; intervals were calculated based on intent-to-treat efficacy visit dates.

Mean dose between visits for a patient was computed as the number of capsules taken from day of previous visit until day before current visit, divided by number of days since previous visit.

Appendix 7.2.10.3.4
NON-U.S. STUDY 84023
MEAN CHANGE FROM BASELINE IN TOTAL HAM-D 21
INTENT-TO-TREAT GROUP
OBSERVED CASE ANALYSIS

Treatment Group	Baseline		Visit 6		LOCF ENDPOINT	
	N	Mean	N	Mean	N	Mean
Org 3770	44	25.6	35	-14.2	44	-10.9
Placebo	45	26.0	33	-11.9	45	-9.0

Visit 6: Days 35 - 48

At baseline: N = number of patients with postbaseline data and mean = mean value of the variable.

Postbaseline: N = number of patients with postbaseline data at a visit, mean = mean change from baseline.

TWO-SIDED p-VALUES FOR PAIRWISE COMPARISONS

	Visit 6	LOCF ENDPOINT
Org 3770 Versus Placebo p-Values		
Wilcoxon Rank Sum Analysis p-Value	0.251	.382
One-Way ANOVA p-Value	0.252	.347

Appendix 7.2.10.3.5
NON-U.S. STUDY 84023
MEAN CHANGE FROM BASELINE IN HAM ITEM 1: MOOD
INTENT-TO-TREAT GROUP
OBSERVED CASE ANALYSIS

Treatment Group	Baseline		Visit 6		LOCF ENDPOINT	
	N	Mean	N	Mean	N	Mean
Org 3770	44	2.89	35	-1.40	44	-0.98
Placebo	45	2.78	33	-1.06	45	-0.82

Visit 6: Days 35 - 48

At baseline: N = number of patients with postbaseline data and mean = mean value of the variable.

Postbaseline: N = number of patients with postbaseline data at a visit, mean = mean change from baseline.

TWO-SIDED p-VALUES FOR PAIRWISE COMPARISONS

	Visit 6	LOCF ENDPOINT
Org 3770 Versus Placebo p-Values		
Wilcoxon Rank Sum Analysis p-Value	0.323	.531
One-Way ANOVA p-Value	0.209	.541

**Appendix 7.2.10.3.6
NON-U.S. STUDY 84023
MEAN CHANGE FROM BASELINE IN MADRS
INTENT-TO-TREAT GROUP
OBSERVED CASE ANALYSIS**

	Baseline		Visit 2		Visit 4		Visit 6		LOCF ENDPOINT	
Treatment Group	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean
Org 3770	54	32.4	54	-7.6	41	-13.9	36	-16.6	54	-13.1
Placebo	52	33.0	52	-6.7	41	-11.5	37	-15.3	52	-9.6

Visit 2: Days 1 - 20

Visit 4: Days 21 - 34

Visit 6: Days 35 - 48

At baseline: N = number of patients with postbaseline data and mean = mean value of the variable.

Postbaseline: N = number of patients with postbaseline data at a visit, mean = mean change from baseline.

TWO-SIDED p-VALUES FOR PAIRWISE COMPARISONS

	Visit 2	Visit 4	Visit 6	LOCF ENDPOINT
Org 3770 Versus Placebo p-Values				
Wilcoxon Rank Sum Analysis p-Value	0.504	0.240	0.902	.167
One-Way ANOVA p-Value	0.587	0.252	0.656	.166

**Appendix 7.2.10.3.7
NON-U.S. STUDY 84023
MEAN CHANGE FROM BASELINE IN GAS
INTENT-TO-TREAT GROUP
OBSERVED CASE ANALYSIS**

	Baseline		Visit 1		Visit 2		Visit 3		Visit 4		Visit 5		Visit 6		LOCF ENDPOINT	
Treatment Group	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean
Org 3770	58	40.9	57	5.6	52	8.7	46	10.8	40	16.4	37	19.7	37	22.0	58	16.3
Placebo	52	40.8	52	4.7	50	7.0	42	11.1	39	13.1	34	17.4	30	19.3	52	13.4

Visit 1: Days 1 - 10

Visit 2: Days 11 - 17

Visit 3: Days 18 - 24

Visit 4: Days 25 - 31

Visit 5: Days 32 - 38

Visit 6: Days 39 - 45

At baseline: N = number of patients with postbaseline data and mean = mean value of the variable.

Postbaseline: N = number of patients with postbaseline data at a visit, mean = mean change from baseline.

TWO-SIDED p-VALUES FOR PAIRWISE COMPARISONS

	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	LOCF ENDPOINT
Org 3770 Versus Placebo p-Values							
Wilcoxon Rank Sum Analysis p-Value	0.236	0.355	0.877	0.146	0.507	0.394	0.378
One-Way ANOVA p-Value	0.338	0.328	0.865	0.158	0.438	0.418	0.324

**Appendix 7.2.11.3.1
NON-U.S. STUDY 85027
DEMOGRAPHIC CHARACTERISTICS**

Treatment Group	N	Age (Years)		Sex [(N%)]	
		Mean	Range	Male	Female
Org 3770	64	40	21-64	23 (36%)	41 (64%)
Placebo	66	41	18-64	20 (30%)	46 (70%)

**Appendix 7.2.11.3.2
NON-U.S. STUDY 85027
BASELINE SEVERITY OF ILLNESS**

Treatment Group	N	HAM D-21	N	HAM Item 1	N	MADRS	N	GAS
Org 3770	64	26.4	64	2.33	64	29.4	64	50.1
Placebo	61	26.2	61	2.21	61	28.4	66	50.9

**Appendix 7.2.11.3.3
NON-U.S. STUDY 85027
DOSING INFORMATION FOR PATIENTS WHO COMPLETED**

		Visit 1		Visit 2		Visit 3		Visit 4		Visit 5	
Treatment Group	N	Mean	STD	Mean	STD	Mean	STD	Mean	STD	Mean	STD
Org 3770	50	20.2	.73	30.1	3.35	40.0	5.33	49.3	10.36	52.1	10.84

Visit 1: Days - 10

Visit 2: Days - 1 - 17

Visit 3: Days 18 - 24

Visit 4: Days 25 - 31

Visit 5: Days 32 - 38

N = Number of patients who completed; intervals were calculated based on intent-to-treat efficacy visit dates.

Mean dose between visits for a patient was computed as the number of capsules taken from day of previous visit until day before current visit, divided by number of days since previous visit.

Appendix 7.2.11.3.4
NON-U.S. STUDY 85027
MEAN CHANGE FROM BASELINE IN TOTAL HAM-D 21
INTENT-TO-TREAT GROUP
OBSERVED CASE ANALYSIS

Treatment Group	Baseline		Visit 2		Visit 4		Visit 5		LOCF ENDPOINT	
	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean
Org 3770	64	26.4	64	-8.4	51	-15.2	51	-14.7	64	-13.4
Placebo	61	26.2	60	-7.5	55	-10.9	48	-11.8	61	-10.9

Visit 2: Days 1 - 20

Visit 4: Days 21 - 31

Visit 5: Days 32 - 38

At baseline: N = number of patients with postbaseline data and mean = mean value of the variable.

Postbaseline: N = number of patients with postbaseline data at a visit, mean = mean change from baseline.

TWO-SIDED p-VALUES FOR PAIRWISE COMPARISONS

	Visit 2	Visit 4	Visit 5	LOCF ENDPOINT
Org 3770 Versus Placebo p-Values				
Wilcoxon Rank Sum Analysis p-Value	0.867	0.006	0.104	.189
One-Way ANOVA p-Value	0.515	0.004	0.083	.124

Appendix 7.2.11.3.5
NON-U.S. STUDY 85027
MEAN CHANGE FROM BASELINE IN HAM ITEM 1: MOOD
INTENT-TO-TREAT GROUP
OBSERVED CASE ANALYSIS

Treatment Group	Baseline		Visit 2		Visit 4		Visit 5		LOCF ENDPOINT	
	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean
Org 3770	64	2.33	64	-0.59	51	-1.27	51	-1.31	64	-1.19
Placebo	61	2.21	60	-0.47	55	-0.76	48	-0.83	61	-0.80

Visit 2: Days 1 - 20

Visit 4: Days 21 - 31

Visit 5: Days 32 - 38

At baseline: N = number of patients with postbaseline data and mean = mean value of the variable.

Postbaseline: N = number of patients with postbaseline data at a visit, mean = mean change from baseline.

TWO-SIDED p-VALUES FOR PAIRWISE COMPARISONS

	Visit 2	Visit 4	Visit 5	LOCF ENDPOINT
Org 3770 Versus Placebo p-Values				
Wilcoxon Rank Sum Analysis p-Value	0.346	0.007	0.011	.027
One-Way ANOVA p-Value	0.373	0.002	0.010	.020

Appendix 7.2.11.3.6
NON-U.S. STUDY 85027
MEAN CHANGE FROM BASELINE IN MADRS
INTENT-TO-TREAT GROUP
OBSERVED CASE ANALYSIS

	Baseline		Visit 2		Visit 4		Visit 5		LOCF ENDPOINT	
Treatment Group	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean
Org 3770	64	29.4	64	-9.3	51	-16.4	51	-17.8	64	-15.7
Placebo	61	28.4	60	-8.0	55	-10.6	48	-12.5	61	-11.6

Visit 2: Days 1 - 20

Visit 4: Days 21 - 31

Visit 5: Days 32 - 38

At baseline: N = number of patients with postbaseline data and mean = mean value of the variable.

Postbaseline: N = number of patients with postbaseline data at a visit, mean = mean change from baseline.

TWO-SIDED p-VALUES FOR PAIRWISE COMPARISONS

	Visit 2	Visit 4	Visit 5	LOCF ENDPOINT
Org 3770 Versus Placebo p-Values				
Wilcoxon Rank Sum Analysis p-Value	0.775	0.004	0.022	.043
One-Way ANOVA p-Value	0.448	0.003	0.013	.020

Appendix 7.2.11.3.7
NON-U.S. STUDY 85027
MEAN CHANGE FROM BASELINE IN THE GAS
INTENT-TO-TREAT GROUP
OBSERVED CASE ANALYSIS

	Baseline		Visit 1		Visit 2		Visit 3		Visit 4		Visit 5		LOCF ENDPOINT	
Treatment Group	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean
Org 3770	64	50.1	63	6.0	64	9.7	58	17.7	52	21.5	51	23.8	64	20.9
Placebo	66	50.9	66	5.3	59	9.5	55	11.4	55	15.1	48	17.5	66	15.2

Visit 1: Days 1 - 10

Visit 2: Days 11 - 17

Visit 3: Days 18 - 24

Visit 4: Days 25 - 31

Visit 5: Days 32 - 38

At baseline: N = number of patients with postbaseline data and mean = mean value of the variable.

Postbaseline: N = number of patients with postbaseline data at a visit, mean = mean change from baseline.

TWO-SIDED p-VALUES FOR PAIRWISE COMPARISONS

	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	LOCF ENDPOINT
Org 3770 Versus Placebo p-Values						
Wilcoxon Rank Sum Analysis p-Value	0.620	0.945	0.013	0.026	0.073	0.063
One-Way ANOVA p-Value	0.677	0.931	0.015	0.030	0.053	0.051

Appendix 8.3.2.1
Adverse Experiences for which $\geq 0.3\%$ of the Org 3770 Treated Patients
were Discontinued in U.S. Short-term Controlled Studies

Body System	Adverse Experience (COSTAK. Term)	Org 3770 (n=453) Number (%)	Placebo (n=361) Number (%)
Body as a Whole	Asthenia	4 (0.9)	1 (0.3)
	Chest Pain	2 (0.4)	1 (0.3)
	Headache	5 (1.1)	3 (0.8)
Digestive System	Constipation	4 (0.9)	1 (0.3)
	Diarrhea	2 (0.4)	1 (0.3)
	Dry Mouth	2 (0.4)	0
	Increased Appetite	4 (0.9)	0
	Liver Function Tests Abnormal	6 (1.3)	3 (0.8)
	Nausea	7 (1.5)	0
	Leukopenia	2 (0.4)	0
Hemic & Lymphatic System			
Metabolic & Nutritional	Weight Gain	4 (0.9)	1 (0.3)
Nervous System	Confusion	2 (0.4)	0
	Dizziness	3 (0.7)	2 (0.6)
	Nervousness	2 (0.4)	2 (0.6)
	Somnolence	47 (10.4)	8 (2.2)
	Thinking Abnormal	2 (0.4)	0
	Tremor	3 (0.7)	1 (0.3)
Special Senses	Amblyopia	4 (0.9)	0

Patients with adverse experiences related to liver function tests are included under "Liver Function Tests Abnormal".

APPENDIX 8.2
SUMMARY OF PATIENT DEATHS

Study Number	Patient Number	Treatment Group	Age	Sex	Days in Study	Highest Dose (mg)	Cause of Death
003-010	403	Org 3770	61	Male	537	60	Cardiac Failure as a Complication of Asthma
003-010	424	Org 3770	47	Female	40	37.5	Myocardial Infarction
003-010	869	Org 3770	59	Female	67	37.5	Suicide by CO Asphyxiation
84023	109	Org 3770	63	Female	12	25	Suicide by Drowning
84023	112	Org 3770	47	Female	13	NA	Suicide by Amitriptyline, Chlorprothixene & Org 3770 OD
84050	153	Org 3770	51	Male	37	30	Suicide by CO Asphyxiation
84050	165	Org 3770	54	Male	23	60	Suicide by CO Asphyxiation
84072	53	Org 3770	58	Female	55	NA	Suicide by Drowning
85002	213	Org 3770	58	Male	17	10	Suicide by Hanging
85004	111	Org 3770	58	Female	34	50	Cholecystitis
85031	47	Org 3770	61	Female	35	72	Suicide by Hanging
86017	18*	Org 3770	63	Female	71	80	Suicide by Jumping From Building
85006	44	Maprotiline	66	Female	32	125	Suicide by Drowning
85004	59	Maprotiline	59	Female	42	200	Suicide by Hanging

NA = Information is not available.

*This patient is part of the ongoing study.

APPENDIX 8.4.1.1

RATE OF SUICIDES: U.S. STUDIES

Drug	Number of Patients	Patient Years of Exposure	Suicides	Crude Rate	Suicides/100 Patient Years
Org 3770	1299	546.5	1	0.0008	0.18
Placebo	361	59.1	0	0	0
Active Controls	301	104.2	0	0	0

RATE OF SUICIDES: NON-U.S. STUDIES*

Drug	Number of Patients	Patient Years of Exposure	Suicides	Crude Rate	Suicides/100 Patient Years
Org 3770	1126	125.2	7	0.0062	5.59
Placebo	133	11.6	0	0	0
Active Controls	676	91.0	2	0.0030	2.20

- * Patient #18 in Study 86017 (an ongoing study that has not been integrated into the database) committed suicide. This patient is not included in the calculation of mortality rates. The patient was taking Org 3770.

RATE OF SUICIDE ATTEMPTS: U.S. STUDIES

Drug	Number of Patients	Patient Years of Exposure	Suicide Attempts	Crude Rate	Suicides/100 Patient Years
Org 3770	1299	546.5	6	0.0046	1.1
Placebo	361	59.8	0	0	0
Active Controls	301	104.2	0	0	0

RATE OF SUICIDE ATTEMPTS: NON-U.S. STUDIES*

Drug	Number of Patients	Patient Years of Exposure	Suicide Attempts	Crude Rate	Suicides/100 Patient Years
Org 3770	1126	125.2	23	0.025	18.37
Placebo	133	11.6	3	0.0226	25.86
Active Controls	676	91.0	6	0.0089	6.59

- * Patient #23 in Study 82028 attempted suicide by jumping down the stairs. This patient is not included in the calculation of crude rates because exposure data is not available for this study.

APPENDIX 8.5.1.1
INCIDENCE OF ADVERSE CLINICAL EXPERIENCES (≥1%)
IN SHORT-TERM U.S. CONTROLLED STUDIES

Body System Adverse Clinical Experience	Org 3770 (N=453)	Placebo (N=361)	Amitriptyline (N=193)	Trazodone (N=49)
Body as a Whole	117 (25.8%)	98 (27.1%)	58 (30.1%)	25 (51.0%)
Asthenia	34 (7.5%)	17 (4.7%)	21 (10.9%)	6 (12.2%)
Infection	6 (1.3%)	8 (2.2%)	2 (1.0%)	2 (4.1%)
Pain	6 (1.3%)	6 (1.7%)	1 (0.5%)	2 (4.1%)
Flu Syndrome	22 (4.9%)	9 (2.5%)	8 (4.1%)	5 (10.2%)
Headache	50 (11.0%)	57 (15.8%)	30 (15.5%)	10 (20.4%)
Chest Pain	5 (1.1%)	4 (1.1%)	1 (0.5%)	2 (4.1%)
Back Pain	9 (2.0%)	3 (0.8%)	1 (0.5%)	3 (6.1%)
Cardiovascular System	26 (5.7%)	24 (6.6%)	32 (16.6%)	14 (28.6%)
Palpitation	9 (2.0%)	8 (2.2%)	7 (3.6%)	6 (12.2%)
Tachycardia	5 (1.1%)	4 (1.1%)	11 (5.7%)	6 (12.2%)
Postural Hypotension	5 (1.1%)	2 (0.6%)	10 (5.2%)	1 (2.0%)
Digestive System	207 (45.7%)	108 (29.9%)	165 (85.5%)	35 (71.4%)
Increased Appetite	76 (16.8%)	7 (1.9%)	12 (6.2%)	3 (6.1%)
Dyspepsia	13 (2.9%)	9 (2.5%)	40 (20.7%)	6 (12.2%)
Flatulence	6 (1.3%)	4 (1.1%)	3 (1.6%)	5 (10.2%)
Nausea	19 (4.2%)	19 (5.3%)	9 (4.7%)	7 (14.3%)
Dry Mouth	112 (24.7%)	54 (15.0%)	156 (80.8%)	30 (61.2%)
Constipation	57 (12.6%)	24 (6.6%)	50 (25.9%)	12 (24.5%)
Diarrhea	11 (2.4%)	16 (4.4%)	3 (1.6%)	7 (14.3%)
Hemic and Lymphatic System	5 (1.1%)	2 (0.6%)	0	0
Metabolic and Nutritional Disorders	71 (15.7%)	13 (3.6%)	16 (8.3%)	8 (16.3%)
Edema	6 (1.3%)	1 (0.3%)	3 (1.6%)	2 (4.1%)
Peripheral Edema	11 (2.4%)	4 (1.1%)	2 (1.0%)	1 (2.0%)
Weight Gain	54 (11.9%)	6 (1.7%)	13 (6.7%)	2 (4.1%)
Musculoskeletal System	15 (3.3%)	11 (3.0%)	6 (3.1%)	6 (12.2%)
Myalgia	9 (2.0%)	3 (0.8%)	4 (2.1%)	0

APPENDIX 8.5.1.1 (CONTINUED)
INCIDENCE OF ADVERSE CLINICAL EXPERIENCES (≥1%)
IN SHORT-TERM U.S. CONTROLLED STUDIES

Body System Adverse Clinical Experience	Org 3770 (N=453)	Placebo (N=361)	Amitriptyline (N=193)	Trazodone (N=49)
Nervous System	288 (63.6%)	117 (32.4%)	154 (79.8%)	36 (73.5%)
Libido Decreased	6 (1.3%)	4 (1.1%)	6 (3.1%)	2 (4.1%)
Confusion	9 (2.0%)	1 (0.3%)	12 (6.2%)	2 (4.1%)
Dizziness	33 (7.3%)	12 (3.3%)	27 (14.0%)	13 (26.5%)
Abnormal Dreams	19 (4.2%)	5 (1.4%)	3 (1.6%)	3 (6.1%)
Hypertonia	6 (1.3%)	4 (1.1%)	0	1 (2.0%)
Insomnia	17 (3.8%)	21 (5.8%)	2 (1.0%)	0
Nervousness	20 (4.4%)	15 (4.2%)	20 (10.4%)	9 (18.4%)
Somnolence	243 (53.6%)	65 (18.0%)	115 (59.6%)	27 (55.1%)
Thinking Abnormal	15 (3.3%)	4 (1.1%)	8 (4.1%)	4 (8.2%)
Tremor	7 (1.5%)	2 (0.6%)	22 (11.4%)	3 (6.1%)
Respiratory System	26 (5.7%)	21 (5.8%)	14 (7.3%)	10 (20.4%)
Dyspnea	5 (1.1%)	1 (0.3%)	3 (1.6%)	2 (4.1%)
Rhinitis	6 (1.3%)	5 (1.4%)	4 (2.1%)	5 (10.2%)
Pharyngitis	8 (1.8%)	6 (1.7%)	5 (2.6%)	2 (4.1%)
Skin and Appendages	18 (4.0%)	23 (6.4%)	18 (9.3%)	6 (12.2%)
Sweating	5 (1.1%)	3 (0.8%)	6 (3.1%)	0
Special Senses	33 (7.3%)	22 (6.1%)	49 (25.4%)	19 (38.8%)
Amblyopia	11 (2.4%)	6 (1.7%)	29 (15.0%)	5 (10.2%)
Tinnitus	6 (1.3%)	3 (0.8%)	4 (2.1%)	1 (2.0%)
Taste Perversion	6 (1.3%)	3 (0.8%)	14 (7.3%)	3 (6.1%)
Urogenital System	25 (5.5%)	19 (5.3%)	23 (11.9%)	6 (12.2%)
Urinary Frequency	8 (1.8%)	5 (1.4%)	1 (0.5%)	2 (4.1%)
Miscellaneous	4 (0.9%)	8 (2.2%)	3 (1.6%)	1 (2.0%)
Total	377 (83.2%)	234 (64.8%)	185 (95.9%)	48 (98.0%)

APPENDIX B.5.1.4.1
DRUG (ORG 3770 VS. PLACEBO) AND GENDER (MALE VS. FEMALE) ON SELECTED ADVERSE EXPERIENCES *

	Incidence Rate: n (%)		Risk Ratios			C-M-H p-Value	Estimate of Common Relative Risk		Breslow- Day Homo- geneity p-Value
	ORG 3770 (N=453)	Placebo (n=361)	RR _f	RR _m	RR _f / RR _m		Value	95% C.I.	
Body as a Whole Back Pain	9(2.0%)	3 (0.8%)	1.737	3.540	0.491	0.639	0.763	0.247-2.359	0.603
Digestive System Increased Appetite	76(16.8%)	7(1.9%)	10.596	5.309	1.996	0.000	3.066	1.576-4.878	0.314
Metabolic and Nutritional Disorders Edema	6(1.3%)	1(0.3%)	-	0.708	-	0.412	1.925	0.403-9.206	0.064
Metabolic and Nutritional Disorders Peripheral Edema	11(2.4%)	4(1.1%)	3.185	-	-	0.004	10.091	2.105-48.374	0.065
Metabolic and Nutritional Disorders Weight Gain	54(11.9%)	6(1.7%)	10.422	4.248	2.453	0.133	1.463	0.891-2.403	0.259
Musculoskeletal System Myalgia	9(2.0%)	3(0.8%)	2.171	2.832	0.767	0.906	1.071	0.342-3.359	0.849
Nervous System Confusion	9(2.0%)	1(0.3%)	2.606	-	-	0.307	0.522	0.150-1.818	0.235
Nervous System Dizziness	33(7.3%)	12(3.3%)	1.448	4.248	0.341	0.634	0.870	0.490-1.544	0.132
Nervous System Abnormal Dreams	19(4.2%)	5(1.4%)	1.216	-	-	0.517	0.757	0.345-1.708	0.019
Nervous System Somnolence	243(53.6%)	65(18.0%)	2.953	3.030	0.975	0.741	1.028	0.871-1.214	0.976
Nervous System Thinking Abnormal	15(3.3%)	4(1.1%)	6.948	1.652	4.206	0.418	0.697	0.290-1.670	0.233
Nervous System Tremor	7(1.5%)	2(0.6%)	2.606	2.832	0.920	0.462	0.615	0.168-2.249	0.956
Respiratory System Dyspnea	5(1.1%)	1(0.3%)	2.606	-	-	0.605	1.565	0.287-8.534	0.479

*Any adverse experience that Org 3770 incidence rate is greater than 1% and twice or more than placebo incidence rate.

RR_f: Relative Risk for Females - Org 3770 rate in females / Placebo rate in females.

RR_m: Relative Risk for Males - Org 3770 rate in males / Placebo rate in males.

APPENDIX 8.5.1.4.1 (Cont)
DRUG (ORG 3770 VS. PLACEBO) AND AGE GROUP (< 65 vs. ≥ 65 yrs) ON SELECTED ADVERSE EXPERIENCES *

	Incidence Rate: n (%)		Risk Ratios			C-M-H p-Value	Estimate of Common Relative Risk		Breslow- Day Homo- geneity p-Value
	ORG 3770 (N=453)	Placebo (n=361)	RR _A	RR _E	RR _A / RR _E		Value	95% C.I.	
Body as a Whole Back Pain	9(2.0%)	3 (0.8%)	3.596	-	-	0.803	0.773	0.102-5.834	0.064
Digestive System Increased Appetite	76(16.8%)	7(1.9%)	9.722	2.300	4.227	0.477	1.396	0.557-3.500	0.185
Metabolic and Nutritional Disorders Edema	6(1.3%)	1(0.3%)	3.995	-	-	0.409	0.423	0.055-3.267	0.662
Metabolic and Nutritional Disorders Peripheral Edema	11(2.4%)	4(1.1%)	2.930	-	-	0.986	0.982	0.132-7.300	0.078
Metabolic and Nutritional Disorders Weight Gain	54(11.9%)	6(1.7%)	6.792	-	-	0.598	1.347	0.450-4.005	0.563
Musculoskeletal System Myalgia	9(2.0%)	3(0.8%)	3.196	0.767	4.167	0.154	0.351	0.083-1.481	0.356
Nervous System Confusion	9(2.0%)	1(0.3%)	5.593	-	-	0.085	0.282	0.067-1.192	0.597
Nervous System Dizziness	33(7.3%)	12 (3.3%)	1.998	-	-	0.975	0.982	0.315-3.059	0.278
Nervous System Abnormal Dreams	19(4.2%)	5(1.4%)	3.729	1.917	1.945	0.000	0.171	0.030-0.366	0.581
Nervous System Somnolence	243(53.6%)	65(18.0%)	2.834	12.267	0.231	0.311	1.204	0.841-1.722	0.109
Nervous System Thinking Abnormal	15(3.3%)	4(1.1%)	2.597	-	-	0.480	0.597	0.143-2.499	0.441
Nervous System Tremor	7(1.5%)	2(0.6%)	2.397	-	-	0.586	0.562	0.073-4.325	0.575
Respiratory System Dyspnea	5(1.1%)	1(0.3%)	3.995	-	-	0.514	-	-	1.000

* Any adverse experiences that Org 3770 incidence rate is greater than 1% and twice or more than placebo incidence rate.

RR_A: Relative Risk for Adult < 65 yrs - Org 3770 rate in < 65 yrs subjects / Placebo rate in < 65 yrs subjects.

RR_E: Relative Risk for Adult ≥ 65 yrs - Org 3770 rate in ≥ 65 yrs subjects / Placebo rate in ≥ 65 yrs subjects.

**Appendix 8.5.1.5
Other Adverse Events
Observed During the Premarketing Evaluation
of REMERON™**

This section excludes adverse events reported in REMERON™ treated patients listed in Appendix 8.5.1.1. In the tabulations that follow, adverse events as reported by the investigator were classified using a standard COSTART-based Dictionary terminology. Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse events are those occurring on one or more occasions in at least 1/100 patients; infrequent adverse events are those occurring in 1/100 to 1/1000 patients; rare events are those occurring in fewer than 1/1000 patients.

Body as a whole: frequent: malaise, abdominal pain, abdominal syndrome acute; infrequent: allergic reaction, chills, cyst, fever, face edema, neoplasm, intentional overdose, ulcer, photosensitivity reaction, neck rigidity, neck pain, abdomen enlarged; rare: carcinoma, cellulitis, hernia, immune system disorder, chest pain substernal.

Cardiovascular System: frequent: hypertension, vasodilatation; infrequent: vascular disorder, electrocardiogram abnormal, angina pectoris, myocardial infarction, arrhythmia, bradycardia, ventricular extrasystoles, syncope, migraine, hypotension; rare: coronary artery disorder, atrial arrhythmia, bigeminy, vascular anomaly, vascular headache, hemorrhage, pulmonary embolus, cerebral ischemia, pallor, cardiomegaly, cardiovascular disorder, phlebitis, cerebrovascular disorder, left heart failure, varicose vein.

Digestive System: frequent: vomiting, anorexia; infrequent: eructation, glossitis, cholecystitis, tooth disorder, gastrointestinal disorder, nausea and vomiting, periodontal abscess, gingivitis, gum hemorrhage, stomatitis, colitis, rectal disorder, liver function tests abnormal; rare: stools abnormal, tongue discoloration, tooth discoloration, ulcerative stomatitis, salivary gland enlargement, increased salivation, intestinal obstruction, pancreatitis, aphthous stomatitis, cirrhosis of liver, gastritis, gastroenteritis, oral moniliasis, nausea vomiting and diarrhea, tongue edema.

Endocrine System: rare: goiter, hypothyroidism, thyroid disorder.

Hemic and Lymphatic System: infrequent: erythrocytes abnormal; rare: lymphadenopathy, leukopenia, petechia, anemia, thrombocytopenia, lymphocytosis, pancytopenia.

Metabolic and Nutritional Disorders: frequent: thirst; infrequent: dehydration, weight loss; rare: electrolyte abnormality, gout, SGOT increased, healing abnormal, acid phosphatase increased, SGPT increased, diabetes mellitus.

Musculoskeletal System: frequent: myasthenia, arthralgia; infrequent: arthritis, joint disorder, tenosynovitis; rare: pathological fracture, bone neoplasm, osteoporosis fracture, bone pain, myositis, tendon rupture, arthrosis, bone disorder, bursitis.

Nervous System: frequent: hypesthesia, speech disorder, apathy, depression, hypokinesia, vertigo, twitching, agitation, anxiety, amnesia, hypertinesia, paresthesia; infrequent: personality disorder, ataxia, delirium, delusions, depersonalization, dyskinesia, extrapyramidal syndrome, libido increased, CNS stimulation, coordination abnormal, dysarthria, hallucinations, manic reaction, neurosis, dystonia, hostility, reflexes increased, emotional lability, euphoria, paranoid reaction, sleep disorder; rare: aphasia, nystagmus, akathisia, zuper, dementia, diplopia, drug dependence, paralysis, grand mal convulsion, hypotonia, myoclonus, psychotic depression, withdrawal syndrome.

**Appendix 8.5.1.5(Cont.)
Other Adverse Events
Observed During the Premarketing Evaluation
of REMERON™**

Respiratory System: frequent: cough increased, sinusitis; infrequent: epistaxis, bronchitis, asthma, respiratory disorder, voice alteration, pneumonia; rare: asphyxia, nasal disorder, laryngitis, lung disorder, pleural disorder, pneumothorax, hiccup.

Skin and Appendages: frequent: pruritus, rash; infrequent: acne, exfoliative dermatitis, dry skin, skin disorder, herpes simplex, alopecia; rare: urticaria, herpes zoster, skin hypertrophy, nail disorder, hair disorder, furunculosis, seborrhea, skin ulcer.

Special Senses: frequent: eye disorder, abnormal vision; infrequent: eye pain, abnormality of accommodation, conjunctivitis, deafness, keratoconjunctivitis, lacrimation disorder, glaucoma, hyperacusis, ear disorder, ear pain; rare: blepharitis, partial transitory deafness, otitis media, taste loss, parosmia.

Urogenital System: frequent: urinary tract infection, menstrual disorder; infrequent: kidney calculus, cystitis, dysuria, urinary incontinence, urination impaired, urinary retention, vaginitis, hematuria, breast pain, amenorrhea, dysmenorrhea, leukorrhea, impotence, rare: polyuria, urethritis, metrorrhagia, fibrocystic breast, menorrhagia, penis disorder, abnormal ejaculation, testis disorder, breast engorgement, breast enlargement, kidney function abnormal, urinary tract disorder, urinary urgency, urine abnormality, prostatic disorder.

APPENDIX 8.5.2.1.1
INCIDENCE OF CLINICALLY SIGNIFICANT BLOOD CHEMISTRY ABNORMALITIES:
SHORT-TERM U.S. CONTROLLED STUDIES *

Laboratory Test (Units)	Criteria for Clinically Significant Abnormal Values	Org 3770 (N=424)	Placebo (N=328)	Amitriptyline (N=181)	Trazodone (N=46)	P-Value ** Org 3770 vs. Placebo
Albumin (g/dL)	20% below LNL	0	0	0	0	-
	20% above UNL	0	1(<1%)	0	0	0.44
BUN (mg/dL)	≥30 mg/dL	1(<1%)	2(1%)	0	0	0.58
Calcium (mg/dL)	10% below LNL	0	1(<1%)	0	0	0.44
	10% above UNL	0	0	0	0	-
Serum Chloride (mEq/L)	10% below LNL	1(<1%)	1(<1%)	0	0	1.00
	10% above UNL	0	0	0	0	-
Cholesterol (mg/dL)	20% below LNL	2(<1%)	2(1%)	2(1%)	0	1.00
	20% above UNL	64(15%)	24(7%)	14(8%)	0	<u>≤0.001</u>
Creatinine (mg/dL)	≥2 mg/dL	1(<1%)	0	0	0	1.00
Globulin (g/dL)	20% below LNL	6(1%)	2(1%)	0	1(2%)	0.45
	20% above UNL	7(2%)	7(2%)	0	4(9%)	0.79
Serum Glucose (mg/dL)	20% below LNL	6(1%)	5(2%)	4(2%)	0	1.00
	20% above UNL	24(6%)	20(6%)	9(5%)	3(7%)	0.88
Phosphorus (mg/dL)	10% below LNL	2(<1%)	6(2%)	4(2%)	1(2%)	0.09
	10% above UNL	7(2%)	4(1%)	0	0	0.76
Serum Potassium (mEq/L)	10% below LNL	2(<1%)	2(1%)	0	0	1.00
	10% above UNL	11(3%)	4(1%)	4(2%)	0	0.20
AST (SGOT)(U/L)	≥3 X UNL	2(<1%)	0	2(1%)	1(2%)	0.51
ALT (SGPT) U/L)	≥3 X UNL	8(2%)	1(<1%)	3(2%)	1(2%)	0.09
LDH (U/L)	≥3 X UNL	0	0	0	0	-
Total Protein (g/dL)	20% below LNL	0	0	1(1%)	0	-
	20% above UNL	0	0	0	0	-
Total Bilirubin (mg/dL)	≥2mg/dL	0	0	0	0	-
Triglycerides (mg/dL)	≥500 mg/dL	25(6%)	9(3%)	6(3%)	0	<u>0.05</u>
Serum Uric Acid (mg/dL)	≥10.5 mg/dL (male)	0	0	2(1%)	0	-
	≥8.5 mg/dL (female)	1(<1%)	2(1%)	0	0	0.58

UNL=Upper Normal Limit

LNL = Lower Normal Limit

N = Number of patients with at least one post-baseline laboratory assessment.

* Studies 003-002, 003-003, 003-008, 003-020, 003-021, 003-022, 003-023, 003-024.

** Fisher's Exact Test (2-Tailed); Statistically significant at p < =0.05.

APPENDIX 8.5.2.1.2
SUMMARY STATISTICS OF SELECTED LABORATORY PARAMETERS:
SHORT TERM U.S. CONTROLLED STUDIES

Laboratory Parameter (Units)		Org 3770	Placebo	Amitriptyline	P-value Org vs Pbo
Cholesterol (mg/dl)					
Baseline	N	453	361	193	-
	Mean	207.8	209.4	211.8	
Week 3	N	279	258	151	0.001
	Mean Change	6.24	-0.28	6.13	
Week 6	N	228	197	127	0.012
	Mean Change	4.34	-1.75	6.09	
Endpoint	N	453	361	193	<0.001
	Mean Change	5.79	-0.80	4.55	
Triglycerides (mg/dl)					
Baseline	N	453	361	193	-
	Mean	165.2	164.2	149.7	
Week 3	N	275	257	149	0.004
	Mean Change	24.05	-2.16	11.43	
Week 6	N	226	197	126	0.008
	Mean Change	29.77	-4.09	20.98	
Endpoint	N	453	361	193	0.001
	Mean Change	21.45	-3.74	14.45	
ALT (U/L)					
Baseline	N	453	361	193	-
	Mean	23.5	22.0	23.0	
Week 3	N	280	258	151	<0.001
	Mean Change	8.92	0.34	1.95	
Week 6	N	228	196	127	0.007
	Mean Change	4.22	-0.30	1.31	
Endpoint	N	453	361	193	<0.001
	Mean Change	4.76	-0.64	1.63	

APPENDIX 8.5.2.1.2 (Cont.)
SUMMARY STATISTICS OF SELECTED LABORATORY PARAMETERS:
SHORT TERM U.S. CONTROLLED STUDIES

Laboratory Parameter (Units)		Org 3770	Placebo	Amitriptyline	P-value Org vs Pbo
AST (U/L)					
Baseline	N	453	361	193	-
	Mean	22.6	21.1	23.2	
Week 3	N	280	258	151	<0.001
	Mean Change	4.33	-0.28	2.11	
Week 6	N	228	197	127	0.145
	Mean Change	1.72	-0.34	-1.54	
Endpoint	N	453	361	193	0.010
	Mean Change	2.22	-0.36	-0.73	
LDH (U/L)					
Baseline	N	453	361	193	-
	Mean	134.7	135.4	139.5	
Week 3	N	279	258	151	0.136
	Mean Change	4.32	0.84	2.41	
Week 6	N	227	195	127	0.405
	Mean Change	2.99	0.81	-0.28	
Endpoint	N	453	361	193	0.004
	Mean Change	4.26	-0.59	0.86	
Alkaline Phosphatase (U/L)					
Baseline	N	453	361	193	-
	Mean	76.1	75.2	65.1	
Week 3	N	279	258	151	0.166
	Mean Change	1.07	-0.70	3.79	
Week 6	N	228	195	127	0.039
	Mean Change	0.87	-3.25	6.65	
Endpoint	N	453	361	193	<0.001
	Mean Change	1.82	-2.53	5.57	

APPENDIX 8.5.2.1.3
LIST OF PATIENTS WITH CLINICALLY SIGNIFICANT
INCREASES IN LIVER ENZYMES

Study	Patient	Age	Sex	Mirt. mg/d	Days	Comments
Serious Cases						
003-010	1051	37	F	40	162	PT* due to liver enzyme elevations (GGT 560, SGPT 280, SGOT 1380, and LDH 1900). 4 days after stopping Org 3770, the patient's enzymes had decreased close to normal levels, but patient suffered massive GI bleeding from a large gastric ulcer and was hospitalized in a coma. She regained consciousness but suffered anoxic brain damage; she was placed in a home and died several months later.
Symptomatic Cases						
003-003	29	29	M	20	13	PT due to symptomatic (diarrhea, fever, and nausea) chemical hepatitis. Lab findings showed leukopenia and clinically significantly elevated liver enzymes (ALT 46, AST 31 at baseline and 506 and 351 at day 16, respectively). The WBC and the biochemical hepatitis (elevated liver enzymes) returned to normal limits by 21 and 42 days after stopping the drug, respectively. A hepatitis panel was negative.
> 5 Fold Enzyme Elevation From Baseline						
003-010	283	30	M	37.5	16	PT because of elevated SGOT (175) and SGPT (431). The elevations began at day 8 (15 mg/day) and reached clinically significant levels by day 14 at a dose of 30 mg/day. The investigator, not aware of the laboratory results, again increased the dose of Org 3770 to 37.5 mg/day for two days before the patient was discontinued from the study. The liver enzyme levels increased for 7 more days after the drug had been discontinued (study day 21), but were normal by day 45. The only concomitant medication was Tylenol 500 mg for headache.
003-010	137	44	M	60	238	PT. From study day 59 until discontinuation, the patient's liver enzymes were found to be significantly high (maximum values for SGPT of 181 and for GGT of 826).

Liver Enzyme units are IU/L.

PT*=premature termination.

APPENDIX 8.5.2.1.3 (CONTINUED)
LIST OF PATIENTS WITH CLINICALLY SIGNIFICANT
INCREASES IN LIVER ENZYMES

Study	Patient	Age	Sex	Mirt. mg/day	Days	Comments
> 5 Fold Enzyme Elevation From Baseline (cont)						
85031	172	31	M	64	17	PT due to elevated LDH (329), SGOT (119), and SGPT (404).
003-010	219	30	M	15	203	PT for increased liver enzymes (SGOT: 278 IU/L and SGPT: 106 IU/L). He also had a clinically significant elevation in SGPT (150 IU/L) on study day 14, at a dose of 7.5 mg/day. This patient also had below-the-normal-range counts of WBCs and neutrophils (see hematology)
	392	35	M		279	PT for marked elevation of liver enzymes (LDH 1130, SGPT 1255, and SGOT 1815). A blood sample taken three days later showed liver enzymes somewhat elevated but returning to normal. Evaluation ruled out a viral infection. The patient admitted to heavy alcohol intake the prior week. In the nine months prior to this event, he had only two episodes of slightly elevated GGT levels.
003-010	842	26	M	15	21	PT because of clinically significant increases in liver enzymes (SGPT 203, SGOT 89). At day 39 the patient was <u>rechallenged</u> after the enzyme levels had decreased (still borderline high), the enzyme levels increased more modestly, but the patient was continued on the study. On day 152 he had normal levels, but they fluctuated until end of study (day 403) when it was normal.

APPENDIX 8.5.2.1.3 (CONTINUED)
LIST OF PATIENTS WITH CLINICALLY SIGNIFICANT
INCREASES IN LIVER ENZYMES

Study	Patient	Age	Sex	Mirt. mg/day	Days	Comments
3-5 Fold Enzyme Elevation From Baseline						
003-010	858	32	M	37.5	34	Patient with history of cocaine and alcohol abuse in the past, had baseline levels of GGT (115), SGPT (73), SGOT (31), AP (109). The study was interrupted at day 34 while the patient was taking Org 3770 37.5 mg/day, because of clinically significant increases in liver enzymes (GGT 271, SGPT 144, SGOT 81, and AP 138). At day 75 the patient was <u>rechallenged</u> after the enzyme levels had decreased (still borderline high), the enzyme levels increased again, but the patient was continued until end of study (day 328). One month after termination the patient had a liver biopsy which was consistent with chronic persistent hepatitis. In this reviewer's opinion the patient had baseline chronic persistent hepatitis that was exacerbated with treatment, including rechallenge.
003-010	1062	42	M		110	PT due to increases in liver enzyme values (SGPT 150). He experienced increased but fluctuating levels from day 14 on. A month after discontinuation he had normal levels.
The other cases with less dramatic enzyme elevations leading to premature terminations in the Org 3770 treated groups are: patient #s 117, 340, 342, 363, 365, 379, 615, 638, 706, 724, 803 (in Study 003-010), 103 (in Study 003-008), 2 (in Study 003-021), 14 (in Study 003-003), 96 (in Study 003-028). Also with minor elevation, but listed under serious adverse events, is patient #104 from Study 84072.						

APPENDIX 8.5.2.1.3 (CONTINUED)
LIST OF PATIENTS WITH CLINICALLY SIGNIFICANT
INCREASES IN LIVER ENZYMES

Study	Patient	Age	Sex	Mirt. mg/day	Days	Comments
Prematurely Terminated Cases Under Other Adverse Events But Of Interest To The Hepatotoxicity Review						
003-010	936	59	M	45	406	PT due to increased anxiety and alcohol use which caused an increase in liver enzyme values (SGPT 119).
003-010	648	58	F		150	PT because of lack of efficacy. At screening, the patient's GGT level was clinically significantly high. GGT levels remained high and on study day 59, GGT levels worsened to 262 and SGPT was elevated to 88. During the remainder of the study, sporadic high levels of these enzymes were observed. The patient drank alcohol "socially."
003-010	837	40	M	30	31	Patient lost to follow-up . At baseline the patient had borderline high increases in liver enzymes (SGPT 72). At day 31 the SGPT was 169.
003-010)	908	43	F	15	28	Patient had her treatment interrupted at 4 weeks, because of clinically significant increases in liver enzymes (SGPT 148). A month later the patient was <u>rechallenged</u> after the enzyme levels had decreased and this time there were no increases.
In this category also fall other cases with less dramatic enzyme elevations: patients # 170, 202, 224, 255, 664 (from Study 003-010).						
The 2 placebo premature termination cases include one (patient #74, study 003-003) with minimal elevation of SGOT and SGPT (46 and 64 IU/L, respectively), while the other case (patient #69, study 003-023) at day 21 of therapy had Alkaline phosphatase levels of 158, LDH of 408, SGOT of 118 and SGPT of 195. The 2 active control patients include: (i) Patient #42, (Study 003-023), a 62-year-old-female on trazodone experienced liver enzyme elevation (SGOT 205, SGPT 369, LDH 256 and alkaline Phosphatase 252) at last assessment day of the 6 week study. The levels were normal 21 days after stopping treatment; (ii) Patient #163, (Study 85004), a 36-year-old-male on maprotiline, presented with nausea and vomiting on day 12 of treatment. On day 13 his SGPT was 265 and SGOT 145. The drug was withdrawn and levels normalized.						

APPENDIX 8.5.2.2.1
INCIDENCE OF CLINICALLY SIGNIFICANT HEMATOLOGY ABNORMALITIES:
SHORT-TERM U.S. CONTROLLED STUDIES *

Laboratory Test (Units)	Criteria for Clinically Significant Abnormal Values	Org 3770 (N=424)	Placebo (N=328)	Amitriptyline (N=181)	Trazodone (N=46)	P-Value ** Org 3770 vs. Placebo
Hemoglobin (g/dL)	≤ 11.5 g/dL (male)	0	1(<1%)	0	0	0.44
	≤ 9.5 g/dL (female)	2(<1%)	0	0	0	0.51
Hematocrit (%)	$\leq 37\%$ (male)	1(<1%)	2(1%)	0	0	0.58
	$\leq 32\%$ (female)	3(1%)	2(1%)	1(1%)	0	1.00
WBC ($\times 10^3/\mu\text{L}$)	$\leq 2.8 \times 10^3/\mu\text{L}$	2(1%)	1(<1%)	0	2(4%)	1.00
	$\geq 16 \times 10^3/\mu\text{L}$	1(<1%)	0	0	0	1.00
Neutrophils (%)	$\leq 15\%$	1(<1%)	0	0	0	1.00
Eosinophils (%)	$\geq 10\%$	5(1%)	3(1%)	11(6%)	1(2%)	1.00
Platelets ($\times 10^3/\mu\text{L}$)	$\leq 75 \times 10^3/\mu\text{L}$	2(<1%)	0	0	0	0.51
	$\geq 700 \times 10^3/\mu\text{L}$	0	0	0	0	0

UNL = Upper Normal Limit

LNL = Lower Normal Limit

N = Number of patients with at least one post-baseline laboratory assessment.

All Hematology parameters, chloride and globulin were missing for one Org patient, therefore N=423. Hemoglobin, Hematocrit and Platelets were missing for one placebo patient, therefore N=327.

* Studies 003-002, 003-003, 003-008, 003-020, 003-021, 003-022, 003-023, 003-024.

** Fisher's Exact Test (2-Tailed); Statistically significant at $p < 0.05$.

APPENDIX 8.5.2.2.2
SUMMARY STATISTICS OF SELECTED LABORATORY PARAMETERS:
SHORT TERM U.S. CONTROLLED STUDIES

Laboratory Parameter (Units)		Org 3770	Placebo	Amitriptyline	P-value Org vs Pbo
WBC COUNT (x 10 ³ /μL)					
Baseline	N	453	361	193	-
	Mean	7.4	7.6	7.4	
Week 3	N	324	275	152	NS
	Mean Change	-0.24	-0.24	-0.24	
Week 6	N	227	198	127	NS
	Mean Change	-0.22	-0.28	-0.27	
Endpoint	N	453	361	193	NS
	Mean Change	-0.28	-0.30	-0.28	
NEUTROPHILS (%)					
Baseline	N	453	361	193	-
	Mean	60.3	60.8	59.7	
Week 3	N	325	275	151	0.004
	Mean Change	-2.37	-0.52	0.82	
Week 6	N	227	198	127	0.219
	Mean Change	-1.94	-0.90	-0.58	
Endpoint	N	453	361	193	0.047
	Mean Change	-1.96	-0.80	-0.45	
BANDS (%)					
Baseline	N	439	348	193	-
	Mean	0.2	0.3	0.7	
Week 3	N	313	266	151	0.323
	Mean Change	0.0	-0.08	-0.54	
Week 6	N	221	194	127	0.036
	Mean Change	0.05	-0.15	-0.49	
Endpoint	N	453	348	193	0.051
	Mean Change	0.02	-0.10	-0.32	
EOSINOPHILS (%)					
Baseline	N	453	361	193	-
	Mean	2.1	2.2	2.6	
Week 3	N	325	274	151	0.019
	Mean Change	0.41	0.04	0.38	
Week 6	N	227	198	127	<0.001
	Mean Change	0.58	-0.15	0.47	
Endpoint	N	453	361	193	<0.001
	Mean Change	0.44	-0.02	0.40	

APPENDIX 8.5.2.2.3
LIST OF PATIENTS WITH WBC ABNORMALITIES

Study	Patient	Age	Sex	Dose mg/d	Days	Comments
003-010	124*	60	F	60	413	Chronically low WBC; 2.58 and 1.17
	167	38	F	60	112	PT** at patient request; Fluctuation of WBC and Neutrophils; 2.93; 0.93
	217	44	F	37.5	30	PT due to low WBC and URI; 2.62 and 1.24
	219	30	M	15	203	Chronically low WBC; 3.01 and 1.58
	232	30	M	60	83	PT due to weight; low neutros at baseline and fluctuations during study; 3.14 and 1.55
	248	35	F	45	41	PT due to thrush; Fluctuation of WBC and Neutrophils; 4.18; 1.55
	278	30	F	30	252	PT due to no effect; Fluctuation of WBC and Neutrophils; 3.57; 1.35
	317	23	M	60	204	PT due to lost to f/u; one episode of low WBC=3.97; 169 days post d/c dx with leukemia.
	357	42	F	60	329	PT due to improv; two episodes of low Neutro; 1.37
	363	49	F	30	127	PT due to LFTs; one episode of low Neutro; 1.56
	408	40	F	60	547	Fluctuation of WBC and Neutrophils; 3.00; 1.23
	416	45	M	45	29	PT due to low WBC and URI; Fluctuation of WBC and Neutrophils; 3.10; 0.86
	420	53	F	15	353	Fluctuation of WBC and Neutrophils; 2.90; 1.23
	562	31	F	30	188	Low WBC and Neutrophils at baseline= 2.93; 1.39; Fluctuation of WBC 3.88
	565	29	F	30	182	Low WBC and Neutrophils at screening= 3.46; 1.94; Fluctuation of WBC and Neutrophils; 3.03; 1.34
	648	58	F	45	150	PT due to no effect; Fluctuation of WBC and Neutrophils; 3.32; 1.49
	664*	53	F	30	97	PT due to neutropenia; A steady decline of WBC and Neutrophils; 3.22; 0.79

*Listed under Serious Adverse Events

WBC and Neutrophil are absolute values with units of $10^3/\mu\text{L}$.

PT**=premature termination.

The end two numbers following the comments discussion are the lowest recorded values for WBC and Neutrophils, respectively.

APPENDIX 8.5.2.2.3 (CONTINUED)
LIST OF PATIENTS WITH WBC ABNORMALITIES

Study	Patient	Age	Sex	Dose mg/day	Days	Comments
003-010	669	58	M	15	94	PT due to decline of WBC; 3.46;2.05
	671*	41	M	60	61	PT due to acute agranulocytosis and infection; A steady decline of WBC and Neutrophils; 3.00; 0.0
	709	27	F	18.75	48	PT due to edema; one episode of low WBC;4.26
	710	33	F	26.25	127	PT due to lost to f/u; Low WBC and Neutrophils at screening =3.87;1.49; Low WBC and Neutrophils at last visit; 3.80;1.49
	719	43	M	60	36	PT due to steady decline of WBC; 3.47
	823	39	F	30	454	PT due to improv; Fluctuation of WBC and Neutrophils;3.65;1.46;
	837	40	M	30	31	PT due to lost to f/u; A steady decline of Neutrophils; 4.82;1.45
	842	26	M	15	403	Fluctuation of WBC; 3.78
	1010	37	M	30	433	PT due to decline of WBC and Neutrophils; 3.24;1.39
	1024	36	M	15	19	PT due to decline of WBC and Neutrophils; 3.27;1.38
85146	224*	59	F	20	9	Hx of Sjogren's; PT due to pancytopenia, agranulocytosis, dermatotoxemia, fever, rash; Needed ICU care;0.60;0.006
85003	168*	41	F	30	14	PT due to leucocytopenia and lymphocytosis; 2.5;0.32
85146	173*	39	F		42	PT due to thrombocytopenia (73 down from baseline of 273.

*Listed under Serious Adverse Events

WBC and Neutrophil are absolute values with units of $10^3/\mu\text{L}$.

PT=premature termination.

The end two numbers following the comments discussion are the lowest recorded values for WBC and Neutrophils, respectively.

APPENDIX 8.5.2.2.3 (CONTINUED)
LIST OF PATIENTS WITH WBC ABNORMALITIES

Study	Patient	Age	Sex	Dose mg/day	Days	Comments
003-003	029*	29	M	20	13	PT due to fever, N/V/D secondary to chemical hepatitis; 2 days later had granulocytopenia; @ baseline WBC=4.3; resolved within a week; 2.50; 1.08
	067	52	M	35	27	PT due to neutropenia (2.16).
003-020 and 003-025	015	34	F	15	85	PT due to tremors; An apparent lab error of WBC assessment of 2.2, Hgb of 7.6, Plts of 43 (day 20) in between two assessments.
003-025	061	32	M	35	70	A switcher from Amit short term. PT due to no effect. Patient with consistently low WBC in both studies. @ baseline WBC=4.4 and neutrophils=1.94. Lowest values on Amit WBC=3.9 and neut=2.0. Lowest on Org 3770 WBC=2.7 and neut=1.0
Controls						
85003	137	27	M	150	33	Doxepin: PT due to mild leucocytopenia (3.5).
85042	024	51	F		15	Amit: PT due to leukopenia (2.5) and thrombocytopenia (184 down from baseline of 242).
86017	046	62	M	112.5	43	Imip: PT due to leucocytopenia and agranulocytosis; 1.4; 0.0
003-008	029	28	F		7	Placebo: PT due to leucocytopenia (2.9) and neutropenia (0.96); at baseline (3.5 and 1.54, respectively).
	118	25	F		40	Placebo: PT due to leucocytopenia (2.7); at baseline (3.2).
003-023	018	59	F		42	Trazodone: Experienced leucocytopenia (2.6) during the study.
	096	55	F	80	7	Trazodone: PT due to other ADR, but had leucocytopenia (2.6) as well.

*Listed under Serious Adverse Events

WBC and Neutrophil are absolute values with units of $10^3/\mu\text{L}$.

PT=premature termination.

The end two numbers following the comments discussion are the lowest recorded values for WBC and Neutrophils, respectively.

APPENDIX 8.5.2.3.1
INCIDENCE OF CLINICALLY SIGNIFICANT LABORATORY ABNORMALITIES
POSTBASELINE: URINALYSIS PARAMETERS*
PLACEBO- AND AMITRIPTYLINE-CONTROLLED U.S. SHORT-TERM STUDIES^b

Laboratory Test	Criteria for Clinically Significant Abnormal Values	Org 3770 (N=176)	Placebo (N=171)	Amitriptyline (N=181)	p-Value ^c Org 3770 Versus Placebo
Urine pH	≤4.6	1 (<1%) ^d	0	0	1.00
	≥8.5	1 (<1%)	2 (1%)	5 (3%)	0.62
Urine Protein	≥300 mg/dL or ≥3+	1 (<1%)	0	0	1.00
Acetone (Ketones)	≥80 mg/dL or ≥3+	0	0	0	-
Urine Glucose	≥500 mg/dL or ≥2+	1 (<1%)	1 (<1%)	1 (<1%)	1.00
Urine RBC	≥10/HPF	9 (5%)	4 (2%)	4 (2%)	0.26
Urine WBC	≥10/HPF	7 (4%)	4 (2%)	9 (5%)	0.54
Urine Casts	≥10/HPF	0	0	0	-

*Patients with multiple postbaseline abnormalities were counted only once in this table.

^bStudies 003-020, 003-021, 003-022, and 003-024.

^cFisher's exact test (two-tailed).

APPENDIX 8.5.3.1
INCIDENCE OF CLINICALLY SIGNIFICANT VITAL SIGN ABNORMALITIES:
SHORT-TERM U.S. CONTROLLED STUDIES *

Vital Sign	Criterion Value *	Change from Baseline *	Org 3770 (N=440)	Placebo (N=353) ^b	Amitriptyline (N=188)	Trazodone N=48	P-Value** Org 3770 vs Placebo
Standing Pulse	≤ 50 bpm	Decrease of ≥15	1 (0.2%)	2 (0.6%)	1 (0.5%)	0	0.59
	≥120 bpm	Increase of ≥15	5 (1.1%)	3 (0.8%)	21 (11.2%)	1 (2.1%)	0.74
Supine Pulse	≤ 50 bpm	Decrease of ≥15	4 (0.7%)	2 (0.6%)	0	0	0.70
	≥120 bpm	Increase of ≥15	3 (0.7%)	0	3 (1.6%)	0	0.26
Standing Systolic BP	≤ 90 mmHg	Decrease of ≥20	7 (1.6%)	5 (1.4%)	11 (5.9%)	3 (6.2%)	1.00
	≥180 mmHg	Increase of ≥20	2 (0.5%)	4 (1.1%)	1 (0.5%)	0	0.42
Supine Systolic BP	≤ 90 mmHg	Decrease of ≥20	8 (1.8%)	5 (1.4%)	1 (0.5%)	7(14.6%)	0.78
	≥180 mmHg	Increase of ≥20	0	0	1 (0.5%)	0	-
Standing Diastolic BP	≤ 50 mmHg	Decrease of ≥15	3 (0.7%)	3 (0.8%)	0	1 (2.1%)	1.00
	≥105 mmHg	Increase of ≥15	11 (2.5%)	8 (2.3%)	9 (4.8%)	0	1.00
Supine Diastolic BP	≤ 50 mmHg	Decrease of ≥15	3 (0.7%)	5 (1.4%)	1 (0.5%)	1 (2.1%)	0.48
	≥105 mmHg	Increase of ≥15	3 (0.7%)	6 (1.7%)	8 (4.3%)	0	0.20
Weight	Gain of ≥7%		33 (7.5%)	0	11 (5.9%)	0	<0.001
	Loss of ≥7%		0	1 (0.3%)	0	1 (2.1%)	0.45

BP = Blood Pressure.

N = Number of patients with at least one post-baseline assessment of the parameters analyzed.

* = To be considered clinically significantly abnormal, a vital sign parameter had to fulfill both of these criteria.

^b = N = 354 for all supine measurements.

* = Studies 003-002, 003-003, 003-008, 003-020, 003-021, 003-022, 003-023, 003-024

APPENDIX 8.5.4.1
LIST OF PATIENTS WITH CARDIOVASCULAR
FINDINGS

Study	Patient	Age	Sex	Mirt. mg/d	Days	Comments
Org 3770 Cases From Uncontrolled Studies						
003-010	716	24	F	45	224	PT* when her ECG tracing showed PVCs/trigeminy. An extensive cardiac work-up (echocardiogram and 24-hour Holter monitor) performed after revealed no cardiac pathology. The patient's history was remarkable for obesity, smoking and hypertension, and she was on hydrochlorothiazide, robitussin, ampicillin, and hormone replacement therapy.
003-010	841	67	M	37.5	27	PT because of T wave inversions on the ECG (indicating ischemia). A stress test demonstrated absence of cardiac disease. Follow-up ECGs were normal.
003-010	928	60	F	37.5	28	Patient with history of hypertension on metoprolol and moduretic, was PT when her ECG revealed bradycardia and ventricular bigeminy. A follow-up ECG, 2 weeks after stopping study medication still showed ventricular bigeminy. The anti-hypertensive medications were changed to verapamil; one month after termination, the ECG was repeated and assessed to be normal with occasional PVCs.
003-010	826	55	F	7.5	1	Patient with history of intermittent palpitations, mitral valve prolapse and hypothyroidism on tenormin and thyroid pills, was PT, when she complained of severe drowsiness and palpitations. The patient's symptoms improved in three days.
003-010	924	40	M	30	52	PT because on the onset of asymptomatic tachycardia (standing pulse of 144 bpm an increase from a baseline of 88 bpm).
003-010	645	53	F	60	103	PT, because she was hospitalized with chest pain and dyspnea. She was diagnosed with a PE. The patient was on hormone replacement therapy.

PT* = premature termination.

APPENDIX 8.5.4.1 (CONTINUED)
LIST OF PATIENTS WITH CARDIOVASCULAR
FINDINGS

Study	Patient	Age	Sex	Mirt. mg/day	Days	Comments
003-010	532	61	M		294	Patient with history of angina, HTN, and DM, was prematurely terminated after 294 days on study medication because of an MI.
003-010	424	47	F	37.5	40	Patient died from acute MI. An autopsy the following day revealed generalized arteriosclerosis with mild involvement of the heart.
003-010	569	51	F	7.5	16	PT because of sedation. The patient had baseline LBBB and on day 15 her ECG was significant for widening of the QRS, that had not resolved 11 days after stopping mirtazapine. The cardiology consultant suggested that it was secondary to "rate dependent" widening and did not recommend further follow-up.
003-010	227	36	F	37.5	30	Patient with a history of HTN and a smoker, suffered cerebral aneurysmal bleed.
Org 3770 Cases From Controlled Studies						
003-020	095	42	M	20	21	Patient had abnormal baseline ECG with an old anteroseptal infarct and non-specific T-wave abnormalities, had a repeat ECG taken after 3 weeks of treatment with Org 3770 (20 mg/day). The ECG indicated possible myocardial ischemia and the patient was terminated from the study.
003-023	129	65	F	15	23	Patient with history of "silent MI", was PT after the ECG revealed complete left bundle branch block (LBBB). She had a normal baseline ECG. An ECG 2 weeks after Org 3770 was discontinued was normal. The patient had complained of tachycardia on day 7. In this reviewer's opinion, the LBBB is possibly drug-related.
003-027	001	39	M	35	777	Patient with HTN, DM, hypercholesterolemia, CAD, and heavy tobacco use, was PT due to an acute anterior MI. An angiogram revealed severely narrowed proximal LAD and he underwent a successful angioplasty.

APPENDIX 8.5.4.1 (CONTINUED)
LIST OF PATIENTS WITH CARDIOVASCULAR
FINDINGS

Study	Patient	Age	Sex	Mirt. mg/day	Days	Comments
Org 3770 Cases From Controlled Studies (cont)						
003-027	079	52	F	35	86	Patient with HTN on isoptin but a normal ECG, was PT after an ECG revealed a complete LBBB. This new finding was still present 1 week after PT.
Active Control Cases From Controlled Studies						
003-022	144	23	F	Amit 280	21	Patient with normal baseline ECG, was PT after she developed a complete LBBB. This change resolved within 1 month.
003-026	040	67	M	Amit	43	Baseline ECG with diffuse, non-specific ST/T wave abnormalities. He was PT after an ECG revealed a RBBB. At the 1-month follow-up visit, the ECG had returned to baseline.
003-027	036	43	F	Amit 160	222	PT for ischemic changes on the ECG with T-wave changes.
003-023	076	61	F	Traz 80	24	Baseline ECG with minor non-specific ST changes. PT when ECG showed slight T-wave inversion anteriorly and patient experienced chest heaviness. A follow-up ECG, performed 6 days after PT showed improvement of the T-wave inversion.
Org 3770 Cases From Phase I Studies						
22503	028	51	M	A volunteer with history of chronic renal failure (CRF) and HTN, received 15 mg of Org 3770 (as a participant in the PK study of mirtazapine in renal insufficiency) and subsequently developed bradycardia (25 bpm), dizziness, nausea, vomiting and general weakness. The ECG showed a sinus nodal bradycardia. Two doses of atropine were administered to reverse the bradycardia. there is a history of previous episodes of exaggerated vasovagal responses.		
88005	006	20	M	Patient #006 (Study , a 20-year-old male volunteer, received 15 mg of Org 3770 orally and 7 mg ¹⁴ C-Org 3770 IV (as a participant in the bioavailability study of mirtazapine) and 4 hours later collapsed. The ECG showed asystole. Pulse and normal rhythm resumed after 4 cardiac compressions. A 12 lead ECG after the event was normal.		

APPENDIX 8.5.4.2
EMERGENCE OF ECG ABNORMALITIES:
SHORT-TERM U.S. STUDIES

ECG	Criterion Value	Change from Baseline	Org 3770 (N=338)	Placebo (N=261)	Amitriptyline (N=168)	p-Value ^b Org 3770 vs Placebo
Heart Rate ^a	<50 bpm	Decrease of ≥15	0	<1.0%	10.0%	ns
	>99 bpm	Increase of ≥15	1.0%	<1.0%	0%	ns
Heart Rate		Decrease of ≥15	3.0%	8.0%	2.0%	ns
		Increase of ≥15	11.0%	4.0%	48.0%	ns
PR	≥200 msec		3.0%	2.0%	1.0%	ns
QRS	≥100 msec		6.0%	7.0%	4.0%	ns
QTc	≥450 msec		7.0%	5.0%	11.0%	ns

N = Number of patients with at least one post-baseline assessment of the parameters analyzed.

^a To be considered clinically significant, a parameter has to fulfill both of these criteria.

^b Fisher's exact test (two-tailed); statistically significant at p<=0.05. (ns=non-significant)

APPENDIX 8.5.4.3
MEAN CHANGES OF ECG ABNORMALITIES:
SHORT-TERM U.S. STUDIES

ECG	Units	Mean Change from Baseline			
		Org 3770 (N=338)	Placebo (N=261)	Amitriptyline (N=168)	p-Value Org 3770 vs Placebo
Heart Rate	bpm	↑ 3.38	↑ 0.75	↑ 13.33	+
PR	msec	↑ 0.8	↑ 1.49	↑ 4.49	ns
QRS	msec	↓ 1.28	↑ 0.66	↑ 1.89	ns
QTc	msec	↑ 4.89	↓ 2.32	↑ 17.09	+

↑ or ↓ = Direction of change

+ = Statistically significant; ns = non-significant.

APPENDIX 8.7.1

Summary of Serious Adverse Events Occurring in Mirtazapine-Treated Patients and Considered Unlikely to be Drug-Related

Study Number	Patient Number	Age	Dose* (mg/d)	Duration (days)	Adverse Event
Cardiovascular Events					
003-010	424	47	38	40	Myocardial Infarction
	532	61	60	294	Myocardial Infarction
	550	50	15	68	Coronary Artery Bypass
	166	73	60	194	Chest Pain
	323	65	30	351	Chest Pain
	645	53	60	103	Pulmonary Embolism
003-027	1	39	35	?	Myocardial Infarction
	71	67	25	?	Transient Ischemic Attack
88013	135	75			Cerebrovascular Disorder
Gastrointestinal Events					
003-010	138	70	0	496	Acute Epigastric Pain
	809	72	15	29	Prostate Cancer
	113	25	15	?	Appendectomy
	119	37	60	550	Surgery For Intestinal Pain
	252	40	60	82	Hemorrhoid Surgery
Miscellaneous					
84072	91	60			Seizure
84008	118	60			Pneumonia
85042	58	53			Pneumonia
003-010	960	50	15	313	Breast Lump
	1031	19	30	363	Pneumothorax
	957	63	8	322	Bone Cancer
	742	38	30	202	Ruptured Disk

*Dose at time of event.

APPENDIX 8.8.1 (Cont.)
Summary of Serious Adverse Events Occurring in Mirtazapine-Treated Patients and Considered Unlikely to be Drug-Related

Study Number	Patient Number	Age	Dose* (mg/d)	Duration (days)	Adverse Event
Miscellaneous					
003-010	634	55	0	405	L Hip Pin Removal
	630	41	60	341	Back surgery
	419	34	45	376	Musculoskeletal Injury
	314	63	60	140	Head Trauma
	275	49	15	531	Abdominal Fistula
	156	21	30	285	Jaw Surgery
	145	36	45	393	Foot Surgery

*Dose at time of event.

OCT 18 1995

Statistical Review and Evaluation

NDA #: 20-415

Applicant: Organon, Inc.

Name of Drug: REMERON (mirtazapine)

Indication: Treatment of Depression

Documents Reviewed: Volumes 1-3, 97-111 and 134-148 submitted 4/29/94. Volumes 1-2 submitted 12/29/94.

Medical Input: Dr. John Balian (HFD-120) was consulted during the review process.

Introduction

The sponsor conducted a total of 32 Phase 3 studies (Table 1) to establish the efficacy and safety of Remeron for the treatment of major depression; 23 short-term studies and 9 long term studies. Of the 23 short-term studies, 14 were placebo-controlled trials and 9 were active-controlled trials. The 9 active-controlled foreign studies will not be reviewed here. Of the 14 short-term placebo-controlled trials, 10 studies will be the primary focus of this review (8 USA studies; Table 2 and 2 foreign studies; Table 3). One foreign placebo-controlled trial (Study 84008) will not be reviewed here because it is a study of the enantiomers of remeron (ORG 4419 and ORG 4420); in all the other studies of the submission, ORG 3770 (the proposed marketing form of remeron) was used. Three short-term studies had too few patients to analyze (less than 15 per group) so these studies were not reviewed.

The long-term studies will be discussed briefly.

Table 1. List of Types of Efficacy Studies

Study Design	# of USA Studies	# of Foreign Studies
Placebo and Active-Controlled Short-term	5	1
Placebo-Controlled Short-term	3	5
Active-Controlled Short-term	0	9
Placebo and Active Controlled Long-term	4	0
Placebo Controlled Long-term	2	0
Active-Controlled Long-term	0	3

Table 2. Remeron Short-term USA Studies

STUDY	INVESTIGATOR/ LOCATION	TREATMENT ARMS	# OF PATIENTS RANDOMIZED	DURATION OF TREATMENT
003-002	Claghorn/ Texas	Remeron Placebo	45 45	6 weeks
003-003	Feighner/ California	Remeron Placebo	45 45	6 weeks
003-008 Fixed Dose	Claghorn/ Texas	Remeron 5 mg Remeron 15 mg Remeron 30 mg Remeron 60 mg Placebo	30 30 30 30 30	6 weeks
003-020	Wakshe Dessain/ Massachusetts	Remeron Amitriptyline Placebo	44 43 43	6 weeks
003-021	Dominguez/ Florida	Remeron Amitriptyline Placebo	50 50 50	6 weeks
003-022	Bremner/ Washington	Remeron Amitriptyline Placebo	50 50 50	6 weeks
003-023	Halikas/ Minnesota	Remeron Trazodone Placebo	50 50 50	6 weeks
003-024	Smith/ Oregon	Remeron Amitriptyline Placebo	50 50 50	6 weeks

Table 3. Remeron Short-term Foreign Studies

STUDY	INVESTIGATOR /LOCATION	TREATMENT ARMS	# OF PATIENTS EVALUATED	DURATION OF TREATMENT
84023	Multicenter/ Finland	Remeron Placebo	60 57	6 weeks
85027	Multicenter/ United Kingdom	Remeron Placebo	64 66	5 weeks

All results presented in this review were produced by this reviewer unless otherwise noted. Inconsistencies between the sponsor's results and this reviewer's results are mentioned. For a complete report of the sponsor's efficacy results as well as tables of demographic and baseline data, see Dr. Balian's medical review. Both Dr. Balian and I have presented tables of reasons for discontinuation. We have used different categories for the reasons in summarizing the data. Dr. Balian combined patients reporting both lack of efficacy (LOE) and adverse event (ADE) as reasons for discontinuation with patients reporting an adverse event as a reason for dropout while this reviewer combined those patients with the patients reporting lack of efficacy. For analysis purposes, this reviewer was interested in identifying all patients reporting lack of efficacy as a reason for dropout; the focus of this review being efficacy evaluation. Dr. Balian's primary focus was safety so that he was more interested in obtaining a reliable count of ADE's.

Design Features of Short-term USA (003) Studies

Patient Population:

All patients in the 003 studies of this submission were outpatients who met DSM III criteria for Major Depressive Disorder (296.2 or 296.3). Males and females over 18 years old were eligible for these trials. According to the protocols for studies 003-002 and 003-003, females were required to be post-menopausal or surgically sterile; the entry criteria were broadened for the other studies to include patients of child-bearing potential using an acceptable form of birth control.

After a 1 week placebo lead-in, to be eligible for randomization into the trial, patients needed to have an HAM-D 17 Total of 18 or greater and less than a 20% change from their screening HAM-D at baseline.

Data used to produce graphics of percentage of patients on study was obtained from Table 3 titled Number and Percent of Patients Discontinuing Treatment by Reason and Week of each study report in Volumes 1 and 2 submitted 12/29/94 and from the database obtained from the sponsor. This reviewer's numbers do not match precisely those presented in Dr. Balian's tables of patient completion rates because his tables are equivalent to the sponsor's Table 2 of each study report where % were computed on the intent-to-treat population not on the randomized population; that is, patients dropping out during the first week of the study without an observation on drug were not included in the denominator by the sponsor (these patients were included in this reviewer's computations of % of patients on study). Also the sponsor treated patients with missing data as not on-study; this reviewer considered any patient who had not discontinued treatment as on-study regardless of their having or not having data at a particular week.

Dose Titration

In all the 003 titration (flexible dose) trials, remeron patients were titrated according to the scheme outlined in the table below. Note that a patient could be maintained on a dose of 10 mg for the duration of the trial; that is, titration was not mandatory.

Week on Study	Max Dose Allowed
1	10 mg
2	20 mg
3-6	35 mg

Dosing data is summarized for all studies on page 48 of this review.

Efficacy Variables

Measures of efficacy used in these trials were the Hamilton Scale for Depression

(HAM-D), the Montgomery and Asberg Depression Scale (MADRS), the Clinical Global Impression scale (CGI severity and global improvement scores) and the Zung Self-rating Depression Scale. These scales were administered weekly. Total scores for both the HAM-D 21 and HAM-D 17 were analyzed by the sponsor but only the results for the HAM-D 21 are reviewed here. The HAM-D 21 total score is considered to be the primary efficacy variable by FDA's Division of Neuropharmacological Drug Products. The sponsor's protocols did not name a specific primary efficacy variable; however, the protocols did state that the analysis of the HAM-D would be the "most detailed" implying its relative importance. The CGI scores, the first item of the HAM-D 21 (the Depressed Mood Item) and the MADRS are considered to be secondary efficacy variables.

The HAM-D 21 consists of 11 items each measured on a scale of 0 to 4 (0 = absent and 4 = severe) and 10 items each measured on a scale to 0 to 2 (0 = absent, 1 = mild, 2 = severe). The scale for the depressed mood item is 0 to 4. The CGI severity of illness score is measured on a 7-point scale (0 = not assessed, 1 = normal, 7 = extremely ill). The CGI global improvement score also is measured on a 7-point scale (0 = not assessed, 1 = very much improved, 4 = no change, 7 = very much worse). The MADRS is a 10 item rating scale with each item scored from 0 to 6 where 6 is indicative of the most severely ill symptom.

All variables were analyzed by the sponsor using the Wilcoxon Rank Sum test and one way analysis of variance (those results are included in Dr. Balian's review). Except where noted, all p-values presented in the tables are the results of Wilcoxon Rank Sum Tests performed by the reviewer. It was necessary to duplicate the sponsor's last-observation-carried-forward (LOCF) analyses because the sponsor only imputed data for those patients who discontinued from the study not for patients missing data. This error occurred due to the sponsor's misinterpretation of a document issued by FDA's Division of Neuropharmacological Drug Products. In addition, during the review process, this reviewer discovered 2 additional errors that precluded using the sponsor's LOCF results; 1) the sponsor included data off drug (after the 6-week treatment period) in their endpoint (Week 6 LOCF) analyses and 2) the sponsor carried forward baseline data for patients with no data on drug. The results of LOCF analyses presented in this review, then, were all performed by this reviewer. All patients with at least one observation on drug were included in the analyses and values were carried forward to impute missing values regardless of the reason for missing.

Study 003-002 (Conducted 2/84 to 4/85)

Study 003-002 is a 6-week placebo-controlled dose titration trial. After a 7 day placebo lead-in, 45 patients were randomized to each treatment arm (placebo or remeron). The average age of the patients was 39.5 years (range of 19 to 61). The number of patients of each gender was about the same in each treatment group and over 90% of the patients were Caucasian. Forty-four (44)% of the remeron patients and 56% of the placebo patients were diagnosed at baseline with recurrent major depression. About 73% of the patients in each group reported frequent weeping (response of 3 on the Depressed Mood Item). Patients were recorded as moderately (~79%) or markedly (~21%) ill at baseline.

Patient Disposition

Of the 45 patients randomized in each group, only 20 (44%) of the placebo patients and 29 (64%) of the remeron patients completed the study (Figure 1). Approximately ¾'s of the patients completed 4 weeks on study so the bulk of the dropouts occurred during Weeks 5 and 6.

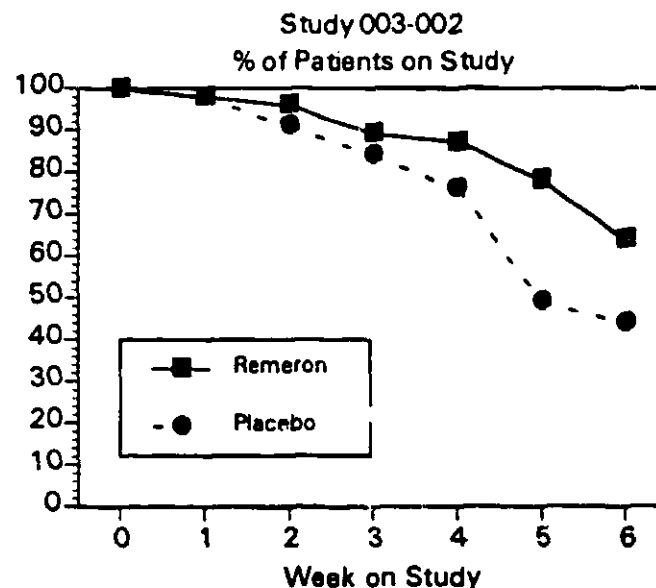


Figure 1

	Randomized	Week 4	Completers
Remeron	45	39 (87%)	29 (64%)
Placebo	45	34 (76%)	20 (44%)

The reasons for study discontinuation are summarized in Table 4. The predominant reason for discontinuation in both groups was lack of efficacy (LOE) with twice as many placebo patients dropping for this reason than remeron patients. About half of the LOE dropouts in both groups discontinued during Weeks 5 and 6. The 4 remeron dropouts who experienced drug-related ADE's discontinued during Weeks 2 and 3.

Table 4. Study 003-002
Reasons for Discontinuation

REASON	Remeron	Placebo
Lack of Efficacy	8 (18%)	20 (45%)
Drug-related ADE	4 (9%)	0 (0%)
Non-drug Related ADE	2 (5%)	2 (5%)
Unknown	2 (5%)	3 (7%)

Efficacy Results

The mean HAM-D 21 results at each week for both observed cases (OC) and the last observation carried forward (LOCF) are depicted in Figure 2 below. The mean change from baseline for the remeron group was statistically significantly greater than the change for the placebo group from Week 1 to Week 4 for both the LOCF and OC analyses.

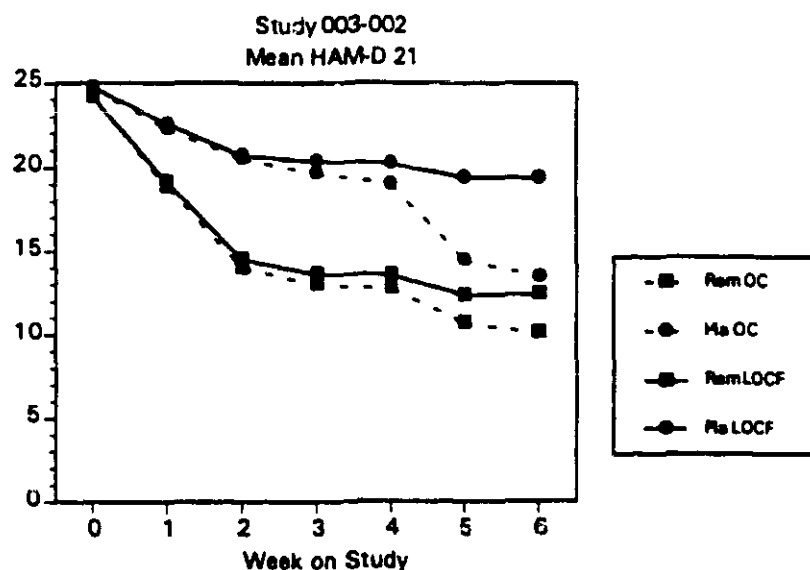


Figure 2

P-values from Comparisons of Change from Baseline by Week

Week	1	2	3	4	5	6
Rem vs PLA						
OC	.04	.001	.002	.007	.23	.30
LOCF	.05	.0006	.0003	.0007	.001	.0008

At Weeks 5 and 6, there is no significant difference between the treatment groups for the observed cases data while the LOCF results produced highly significant results in favor of remeron (Table 5).

Table 5. Study 003-002
Change from Baseline for HAM-D 21 Total at Weeks 4, 5 and 6

	Remeron Mean (SD)	Placebo Mean (SD)	P-value
Baseline	24.2 (3.5) n=44	24.7 (2.9) n=44	.21
Week 4			
OC	-11.5 (8.2) n=36	-5.8 (9.2) n=32	.007
LOCF	-10.6 (8.2) n=44	-4.5 (8.5) n=44	.0007
Week 5			
OC	-13.3 (8.5) n=33	-10.1 (9.4) n=22	.23
LOCF	-11.8 (8.9) n=44	-5.4 (8.7) n=44	.001
Week 6			
OC	-14.5 (8.8) n=26	-11.4 (10.2) n=19	.30
LOCF	-11.7 (8.8) n=44	-5.4 (9.0) n=44	.0008

The difference between the LOCF and OC results is clearly due to the large number of dropouts after Week 4. Figure 3 illustrates the results for patients who completed 4 weeks on therapy compared to patients who completed the study. It is clear that the placebo patients who remain on study continue to improve while the placebo patients who discontinued treatment exhibited a minimal decrease in HAM-D during the first 4 weeks of the study. If we assume that the latter group of patients would not improve if continued on study, we see that dropping these 12 placebo patients from the analysis (OC analysis) biases against the drug. Note also from Figure 3 that remeron dropouts (patients who completed only 4 weeks on study) are doing better than the placebo dropouts. (This was true for dropouts at each week.)

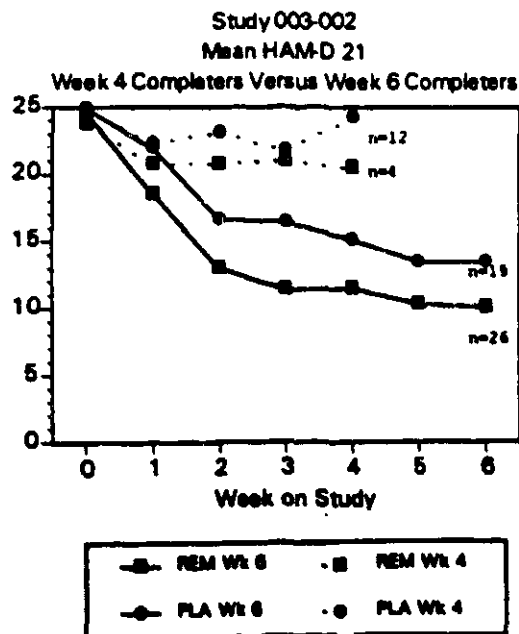


Figure 3

The results for the secondary efficacy variables (Table 6) are consistent with the results for the HAM-D Total. The treatment differences for both OC and LOCF were significant from Week 1 to Week 4 ($p < .001$) for all of the secondary variables. Again the Weeks 5 and 6 OC results showed no statistically significant treatment difference while the Weeks 5 and 6 LOCF results were clearly significant (see Table 6 for Week 6 results). The effects of dropouts on the results, then, is evident for these variables as it was for the HAM-D 21 Total.

Table 6. Study 003-002
Week 6 Efficacy Results for Secondary Endpoints

	Remeron Mean (SD)	Placebo Mean (SD)	P-value
Sample Size			
Week 6 OC	44	44	
Week 6 LOCF	26	19	
HAM-D Item#1			
Baseline	2.9 (0.5)	2.8 (0.5)	.24
Week 6			
OC	-1.9 (1.2)	-1.4 (1.1)	.19
LOCF	-1.5 (1.3)	-0.6 (1.1)	.002
CGI-Severity			
Baseline	4.3 (0.5)	4.2 (0.4)	.20
Week 6			
OC	-1.5 (1.2)	-1.2 (1.3)	.43
LOCF	-1.2 (1.2)	-0.5 (1.2)	.004
Global Improvement			
Week 6			
OC	2.1 (1.2)	2.5 (1.3)	.34
LOCF	2.5 (1.3)	3.3 (1.3)	.002
MADRS			
Baseline	27.9 (4.8)	29.8 (4.2)	.04
Week 6			
OC	-15.0 (12.1)	-13.0 (11.8)	.49
LOCF	-12.8 (11.4)	-6.9 (9.8)	.007

Reviewer's Comments on Study 003-002

The results from Week 1 to Week 4 for the primary efficacy variable (Figure 2) and the secondary efficacy variables (OC and LOCF) showed a statistically significant improvement in depressive symptoms for the remeron patients compared to the placebo patients. At Weeks 5 and 6, the OC results show no difference between the treatment groups for any efficacy measure while the LOCF results continue to significantly favor remeron. The difference between the OC and LOCF results at Weeks 5 and 6 can be

~~ascribed to the large number of dropouts following Week 4 (Figure 1). Patients in both treatment groups primarily dropped due to LOE which is clearly reflected in the small changes in HAM-D-21 observed for these groups (Figure 3). Patients who stay on study continue to improve in both treatment groups. Comparisons within these 2 cohorts (dropouts and completers) show that the remeron patients consistently exhibit a larger mean decrease on their HAM-D 21 Total score than the placebo patients.~~

The positive LOCF results at every week coupled with the fact that the remeron dropouts improved more than the placebo dropouts provide sufficient statistical evidence of remeron's effectiveness at decreasing the symptoms of depression when compared to placebo.

Study 003-003 (Conducted 6/84 to 12/85)

Study 003-003 is a 6-week placebo-controlled dose-titration trial. After a one week placebo lead-in, 45 patients were randomized to each treatment group.

The mean age of the patients was 43 years (range of 19 to 65). The treatment groups were imbalanced as to gender; of the placebo patients, 33% were male while 53% of the remeron patients were male ($p = .05$). More than 95% of the patients were Caucasian. About 1/3 of the patients had a baseline diagnosis of recurrent major depression. More than 85% of the patients in each group reported frequent weeping at baseline (3 on the HAM-D Depressed Mood Item). Sixty-one (61)% of the patients were considered moderately ill at baseline and 35% markedly ill (3 patients were recorded as mildly ill).

Patient Disposition

The dropout rates in the 2 treatment groups were comparable (Figure 4). Almost 80% of the patients in each group completed 4 weeks on study. By Week 6, 62% of the remeron patients and 58% of the placebo patients remained on study.

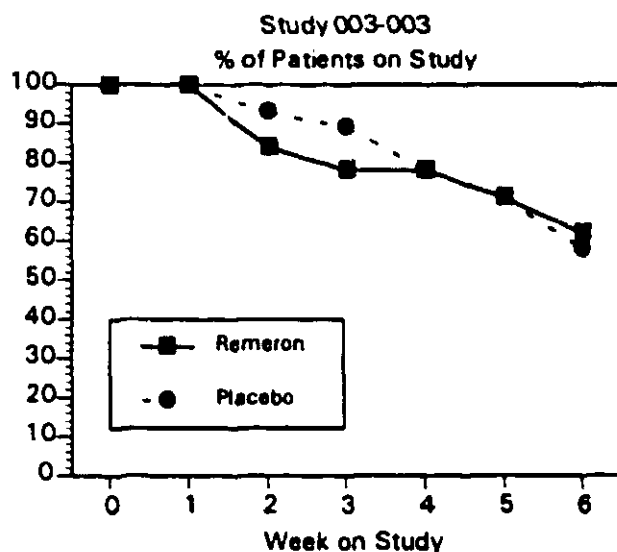


Figure 4

	Randomized	Week 4	Completers
Remeron	45	35 (78%)	28 (62%)
Placebo	45	35 (78%)	26 (58%)

It is interesting to note that more patients in the remeron group dropped due to LOE than in the placebo group (Table 7 on next page); about half of those remeron patients discontinued with less than 3 weeks on therapy. All the placebo LOE dropouts discontinued after more than 3 weeks on study. Five of the 9 remeron patients who dropped due to ADE

(both drug and no-drug related) discontinued during Week 2.

Table 7. Study 003-003
Reasons for Discontinuation

REASON	Remeron	Placebo
Lack of Efficacy	7 (16%)	5 (11%)
Drug-related ADE	5 (11%)	2 (4%)
Non-drug Related ADE	4 (9%)	9 (20%)
Lost to Follow-up	1 (2%)	2 (4%)
Patient Improvement	0 (0%)	1 (2%)

Efficacy Results

No statistically significant treatment difference was observed for any efficacy variable at any timepoint during the trial (Figure 5 and Table 8).

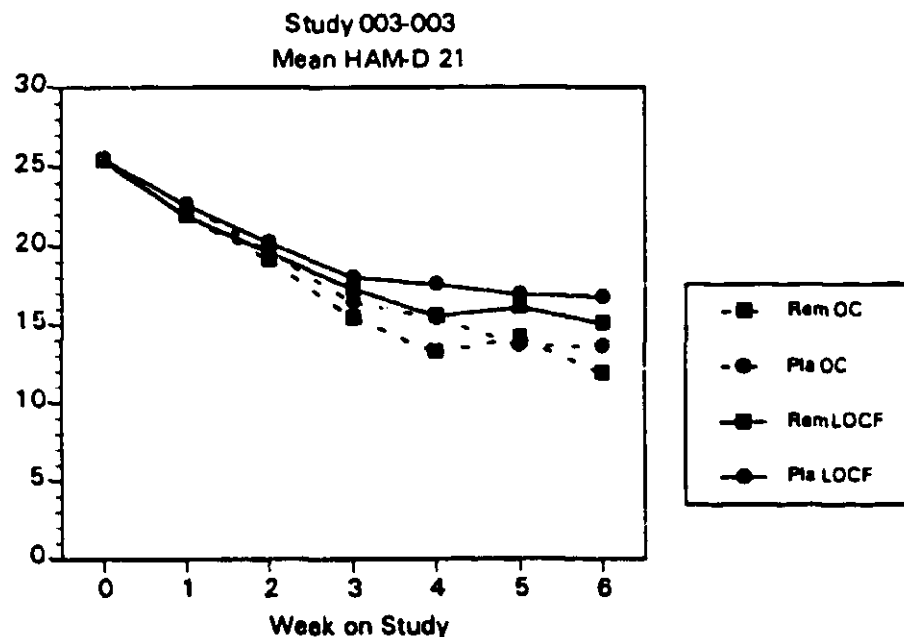


Figure 5

P-values from Comparisons of Change from Baseline by Week

Week	1	2	3	4	5	6
Rem vs PLA						
OC	.15	.73	.32	.14	.91	.51
LOCF	.15	.80	.59	.25	.60	.49

**Table 8. Study 003-003
Week 6 Efficacy Results**

	Remeron Mean (SD)	Placebo Mean (SD)	P-value
Sample Size			
Week 6 OC	45	45	
Week 6 LOCF	27	24	
HAM-D Total			
Baseline	25.4 (4.4)	25.5 (4.1)	.76
Week 6			
OC	-14.0 (7.3)	-11.5 (8.3)	.51
LOCF	-10.4 (8.7)	-8.8 (8.1)	.49
HAM-D Item#1			
Baseline	2.9 (0.3)	2.8 (0.4)	.56
Week 6			
OC	-1.3 (1.0)	-1.2 (1.1)	.71
LOCF	-1.1 (1.0)	-1.0 (1.0)	.55
CGI-Severity			
Baseline	4.3 (0.5)	4.3 (0.6)	.95
Week 6			
OC	-1.4 (1.1)	-1.3 (1.0)	.75
LOCF	-1.1 (1.1)	-1.0 (1.0)	.71
Global Improvement			
Week 6			
OC	2.3 (1.1)	2.3 (1.2)	.86
LOCF	2.8 (1.3)	2.7 (1.0)	.84
W-ADRS			
Baseline	28.5 (5.0)	28.8 (4.2)	.72
Week 6			
OC	-14.0 (8.9)	-10.9 (9.9)	.35
LOCF	-10.3 (9.9)	-7.8 (9.3)	.24

Since a gender imbalance was observed between the treatment groups, this reviewer performed analyses adjusting for gender. The results of those analyses did not differ from what is presented in the table above. This reviewer also examined the relationship between baseline and response and found no benefit of treatment related to severity of illness.

Reviewer's Comments on Study 003-003

The results of this study do not show that remeron is statistically significantly more effective for the treatment of depression than placebo. There appears to be no problems (such as, low dosing [see Dosing section of this review on page 48], excessive dropouts, etc.) which would suggest that the trial was incapable of showing a treatment difference due to the design or conduct of the trial. Due to the absence of an active control group, one cannot ascertain whether the trial failed due to the ineffectiveness of the drug or due to a large placebo response. From a statistical viewpoint, this trial is a negative trial.

Study 003-020 (Conducted 8/86 to 4/90)

Study 003-020 is 6-week 3-armed trial conducted by two investigators; Dr. Dessian (8/86 to 4/88) and Dr. Walshe (4/88 to 4/90). After a 7-day placebo lead-in, 44 patients were randomized to remeron, 43 to amitriptyline and 43 to placebo. The mean age of the patients was 44 years (ranging from 20 to 85). In the remeron and amitriptyline groups, 54% of the patients were male; while, in the placebo group, 38% of the patients were male. More than 90% of the patients were Caucasian.

The groups were comparable at baseline. Approximately half the patients in each treatment group were diagnosed at baseline with recurrent major depression. About 3% of the patients in each group reported frequent weeping at baseline (3 on the Depressed Mood Item). The physician assessed about half of the patients as moderately ill at baseline in each treatment group. Twenty-four (24) % of the placebo patients compared to 5% of the remeron patients were rated as severely ill at baseline.

Patient Disposition

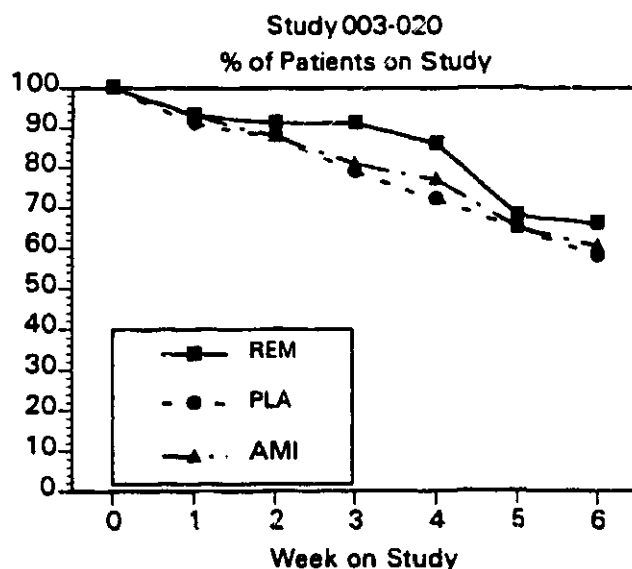


Figure 6

	Randomized	Week 4	Completers
Remeron	44	38 (86%)	29 (66%)
Placebo	43	31 (72%)	25 (58%)
Amitrip.	43	33 (77%)	26 (61%)

As can be seen from Figure 6 above, the dropout rate was nearly constant for the duration of the trial, particularly for the control groups; about 4-6 patients dropped each week for a variety of reasons (Table 9 below). Two-thirds of the remeron patients completed the study while 58% of the placebo patients and 61% of the amitriptyline patients completed.

The same number of patients in each group discontinued due to LOE with most of those occurring during Week 5. Only one remeron-treated patient dropped out of the study due to an ADE, 3 additional remeron patients missed visits due to ADE's but remained on study. By contrast, 16% of the amitriptyline patients dropped due to ADE. Six patients (2

in each group) were lost-to-followup during the first week of the study and one placebo patient never took drug.

Table 9. Study 003-020
Reasons for Discontinuation

REASON	Remeron	Placebo	Amitriptyline
Lack of Efficacy	4 (9%)	4 (9%)	4 (9%)
Drug-related ADE	1 (2%)	2 (5%)	7 (16%)
Non-drug Related ADE	5 (11%)	6 (14%)	3 (7%)
Lost to Follow-up	4 (9%)	3 (7%)	2 (5%)
Patient Improvement	1 (2%)	0 (0%)	1 (2%)
Other	0 (0%)	3 (7%)	0 (0%)

Efficacy Results

The results for the HAM-D 21 Total are shown in Figure 7 below.

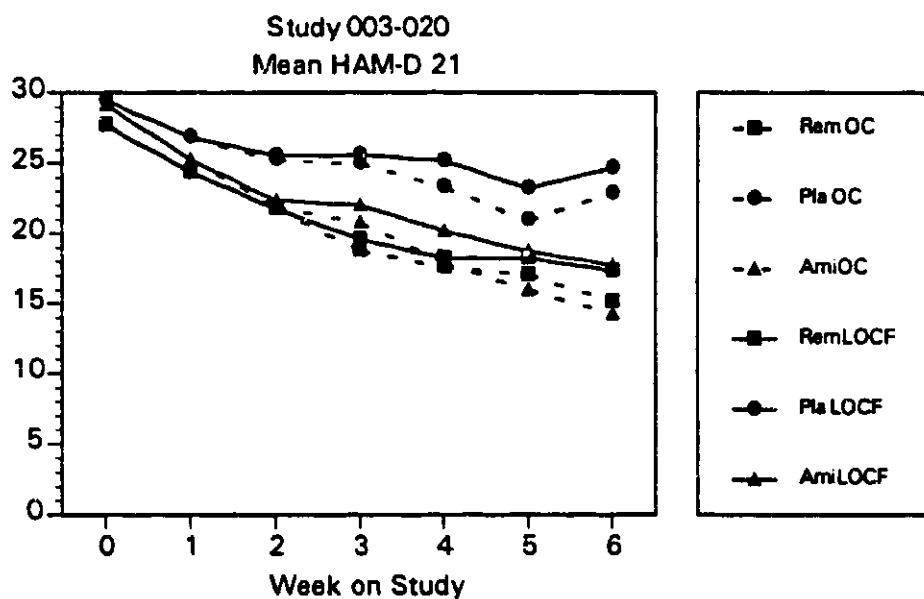


Figure 7

P-values from Comparisons of Change from Baseline by Week

Week	1	2	3	4	5	6
Rem vs PLA OC	.69	.07	.02	.01	.26	.007
OC LOCF	.69	.11	.09	.001	.05	.04
Ami vs PLA OC	.38	.003	.02	.004	.05	.002
OC LOCF	.38	.02	.04	.007	.02	.0009

Remeron significantly reduced the HAM-D 21 total compared to placebo at Weeks 3, 4 and 6 (OC and LOCF). Amitriptyline beat placebo at every week from Week 2 to 6.

Table 10. Study 003-020
Change from Baseline for HAM-D 21 Total at Weeks 4, 5 and 6

	Remeron Mean (SD)	Placebo Mean (SD)	P-value Rem vs Pla	Amitriptyline Mean (SD)
Baseline	27.8 (5.1) n=40	29.5 (6.9) n=39	0.37	29.2 (6.5) n=40
Week 4				
OC	-9.9 (6.4) n=28	-5.5 (6.1) n=30	.01	-10.7 (7.5) n=32
LOCF	-9.5 (7.3) n=39	-4.3 (6.0) n=39	.001	-9.1 (8.0) n=40
Week 5				
OC	-10.8 (6.6) n=25	-8.7 (7.5) n=22	.26	-12.8 (8.8) n=26
LOCF	-9.5 (7.3) n=39	-6.3 (7.7) n=39	.05	-10.5 (8.9) n=40
Week 6				
OC	-13.0 (9.0) n=23	-6.2 (6.5) n=24	.007	-14.4 (8.7) n=25
LOCF	-10.6 (8.7) n=40 ¹	-4.8 (6.4) n=39	.004	-11.5 (9.1) n=40

The lack of significance for Remeron over placebo at Week 5 OC is primarily due to the large placebo response. Four placebo patients had more than a 50% decrease in their HAM-D Total at Week 5 compared to Week 4; all these patients' Week 6 HAM-D's were approximately 50% greater than their Week 5 values and in 1 case larger than the Week 4 value. Clearly then the Week 5 responses of these 4 placebo patients were not sustained.

The results for the secondary variables over time were similar to what was observed for the primary efficacy variable; that is, the responses for remeron were generally positive at Weeks 3, 4 and 6 and, for amitriptyline, at Weeks 2 through 6. The exception was the results of the HAM-D Depressed Mood Item; those results were only significant at Week 6 (OC and LOCF) for both drug groups compared to placebo. The results for Week 6 only are presented in the Table 11 on the following page.

Due to the small p-values for the baseline comparisons ($p < .15$) of the secondary variables, this reviewer performed baseline adjusted analyses. The results of these analyses were consistent with what is presented in the tables.

¹ One patient had only Week 6 data so that patient is included here but not in the Week 4 or 5 LOCF analyses.

Table 11. Study 003-020
Week 6 Efficacy Results for Secondary Endpoints

	Remeron Mean (SD)	Placebo Mean (SD)	P-value Rem vs Pla	Anis:riptyline Mean (SD)
Sample Size				
Week 6 OC	23	24		25
Week 6 LOCF	41	39		40
HAM-D Item#1				
Baseline	2.7 (0.6)	2.9 (0.7)	.13	2.8 (0.5)
Week 6				
OC	-1.3 (0.9)	-0.7 (0.7)	.01	-1.5 (1.3)
LOCF	-1.1 (0.9)	-0.5 (0.7)	.008	-1.2 (1.2)
CGI-Severity				
Baseline	4.5 (0.6)	4.8 (0.8)	.12	4.7 (0.8)
Week 6				
OC	-1.8 (1.3)	-0.8 (0.9)	.006	-2.2 (1.4)
LOCF	-1.5 (1.3)	-0.6 (0.9)	.001	-1.7 (1.5)
Global Improvement				
Week 6				
OC	2.2 (1.0)	2.5 (1.3)	.001	2.1 (1.1)
LOCF	2.5 (1.1)	3.3 (0.9)	.0001	2.5 (1.3)
MADRS				
Baseline	25.8 (5.7)	28.8 (8.5)	.14	27.8 (6.3)
Week 6				
OC	-12.6 (9.6)	-6.6 (7.7)	.05	-14.2 (11.1)
LOCF	-9.4 (10.1)	-4.5 (7.2)	.03	-11.6 (10.8)

Reviewer's Comments on Study 003-020

The results of this study offer statistical evidence of the efficacy of remeron for the treatment of depression compared to placebo. Week 6 OC and LOCF comparisons of remeron to placebo were statistically significant for all efficacy measures. Also, comparisons over time show significant treatment effects as early as Week 3.

Study 003-021 (Conducted 6/88 to 9/88)

Study 003-021 is a 6-week study of 3 treatment groups; remeron, placebo and amitriptyline. A total of 50 patients were randomized to each treatment group.

The mean of age of the patients was 46 years (ages ranged from 18 to 76). Patients were predominantly female (56%) and Caucasian (88%).

About ½ the patients in each treatment group were diagnosed at baseline with recurrent major depression. A little less than half of the patients reported frequent weeping at baseline (3 on the Depressed Mood Item). The majority of the patients (>80%) in each group were rated as moderately ill at baseline.

Patient Disposition

The percentage of patients on study by week for each treatment group is depicted in Figure 8 below.

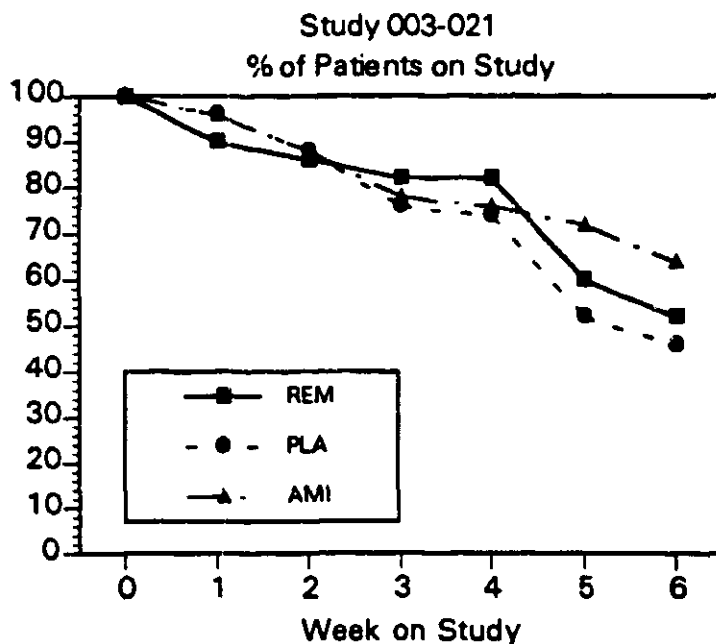


Figure 8

	Randomized	Week 4	Completers
Remeron	50	41 (82%)	26 (52%)
Placebo	50	37 (74%)	23 (46%)
Amitrip.	50	38 (76%)	32 (64%)

At Week 4, more than ¾'s of the patients (82% in the remeron group) were still on study (Figure 8). At the completion of the study, only about half the patients remained; 52% of the remeron patients, 46% of the placebo patients and 64% of the amitriptyline patients. Most of the dropouts in the remeron and placebo groups occurred during the 5th week of the study; 10 remeron patients and 11 placebo patients discontinued at Week 5 due to lack of efficacy (Table 12).

It is interesting to note from Table 12 that the same number of patients (26%) in the remeron group and the placebo group dropped due to lack of efficacy while no patients in the amitriptyline group dropped for this reason.

The 4 remeron patients who discontinued due to drug-related ADE dropped during the first 3 weeks of the study. Amitriptyline ADE dropouts occurred at a steady rate through Weeks 2 to 5.

Table 12. Study 003-021
Reasons for Discontinuation

REASON	Remeron	Placebo	Amitriptyline
Lack of Efficacy	13 (26%)	13 (26%)	0 (0%)
Drug-related ADE	4 (8%)	1 (2%)	6 (12%)
Non-drug Related ADE	5 (10%)	8 (16%)	3 (6%)
Lost to Follow-up	2 (4%)	3 (6%)	6 (12%)

Efficacy Results

Both the LOCF and OC results for the HAM-D 21 for Baseline and Weeks 1 through 6 are illustrated in Figure 9 below.

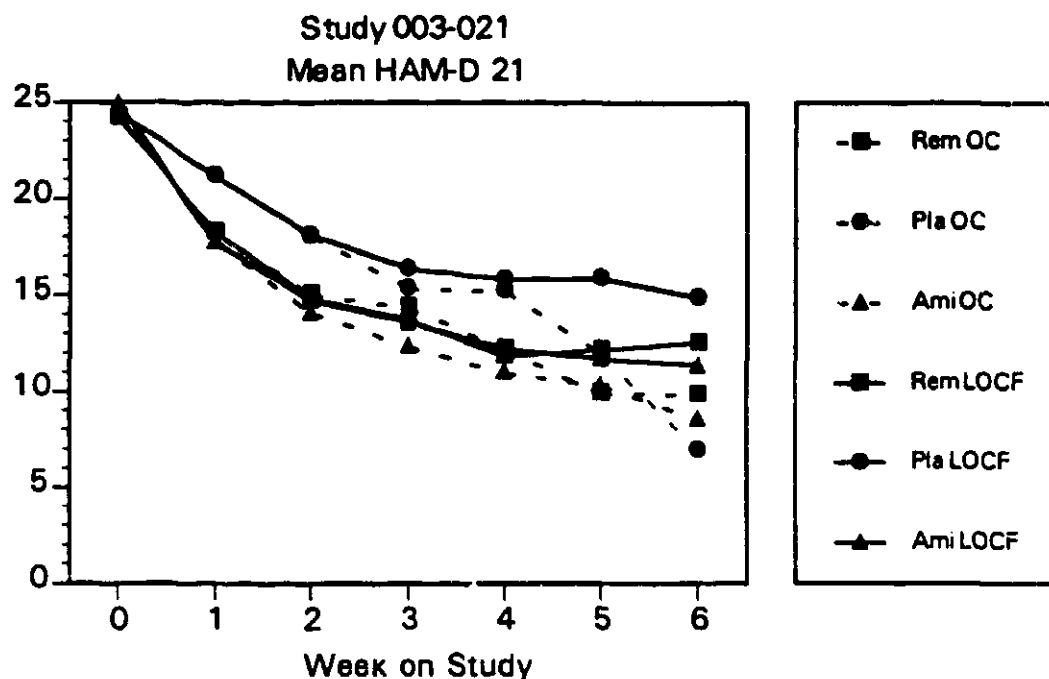


Figure 9

P-values for Comparisons of Change from Baseline By Week						
Week	1	2	3	4	5	6
Rem vs PLA						
OC	.007	.03	.89	.17	.50	.06 ¹
LOCF	.007	.02	.12	.02	.04	.22
Ami vs PLA						
OC	.002	.0009	.09	.02	.30	.93
LOCF	.002	.002	.01	.006	.004	.02

From the figure and table above, it is clear that there are inconsistencies among the remeron-placebo comparisons. Focussing first on the last-observation-carried-forward results (the solid lines of Figure 9), amitriptyline beats placebo at every week while remeron beats placebo at 4 of the 6 weeks (Weeks 1, 2, 4 and 5). It is particularly disconcerting to see that the Week 6 LOCF results are not positive for remeron. Also, note during the last 3 weeks on study, the remeron LOCF means suggest that remeron patients are worsening (Table 13 on the following page).

The OC results show no significant treatment difference for patients who remain on study for 3 weeks or longer. At Week 6 OC, the results favor placebo over remeron.

¹ Results favor placebo.

Table 13. Study 003-021
Change from Baseline for HAM-D 21 Total at Weeks 4, 5 and 6

	Remeron Mean (SD)	Placebo Mean (SD)	P-value Rem vs Pla	Amitriptyline Mean (SD)
Baseline	24.2 (3.7) n=45	24.4 (4.1) n=48	0.37	25.0 (4.3) n=48
Week 4				
OC	-12.1 (7.1) n=39	-9.3 (7.7) n=32	.17	-13.8 (5.8) n=37
LOCF	-12.4 (7.1) n=44	-8.6 (7.9) n=48	.02	-12.8 (6.1) n=48
Week 5				
OC	-14.4 (6.0) n=26	-12.9 (8.2) n=23	.50	-15.0 (7.2) n=31
LOCF	-12.1 (7.4) n=44	-8.5 (8.5) n=48	.04	-13.3 (7.2) n=48
Week 6				
OC	-13.8 (5.9) n=22	-17.4 (5.3) n=21	.06¹	-17.1 (5.6) n=27
LOCF	-11.7 (7.6) n=45 ¹	-9.5 (8.9) n=48	.22	-13.6 (7.2) n=48

If we focus now on the patients who completed the study, we see that the remeron completers appear to be worsening during the last 2 weeks of the study while the control groups continue to show improvement (Figure 10).

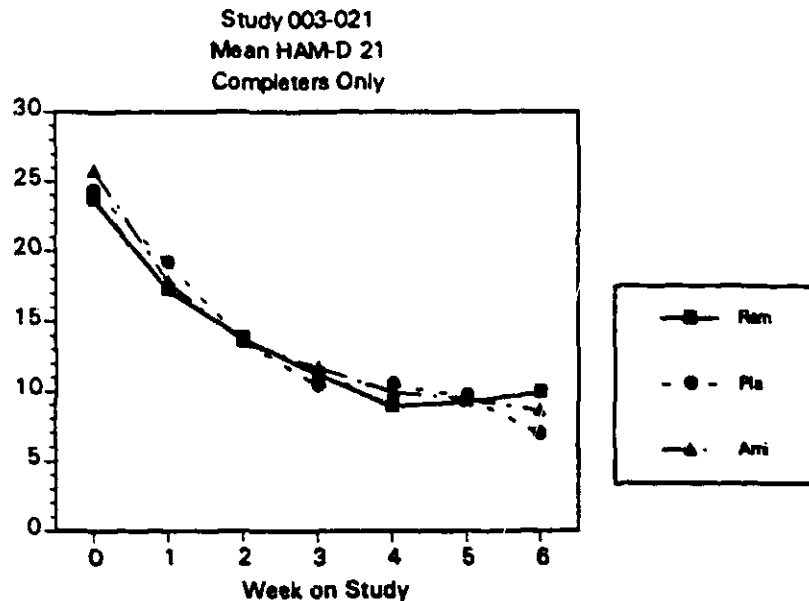


Figure 10

¹ One patient had only Week 6 data so that patient is included here but not in the Week 4 or 5 LOCF analyses.

² Results favor placebo.

The table below shows the number (%) of completers who showed improvement between Week 4 and Week 6 (improvement is defined as a decrease in the HAM-D 21 Total). It is clear from this data that more patients on placebo and amitriptyline improved than patients on remeron. So the lack of significance at Week 6 for both LOCF and OC appears to be due to both worsening in the remeron group and improvement in the placebo group.

Week 6 Completers Who Improved Between Week 4 and Week 6

	Remeron	Placebo	Amitriptyline
% Patients Improved	36%	57%	70%

The improvement for placebo completers is particularly striking (this improvement was observed for all the secondary variables as well which can be seen in Table 14 on the following page). Figure 11 illustrates the course of change in HAM-D 21 for 3 sets of completers; it can be seen that the Week 6 placebo completers show appreciable improvement from Week 1 to the completion of the study.

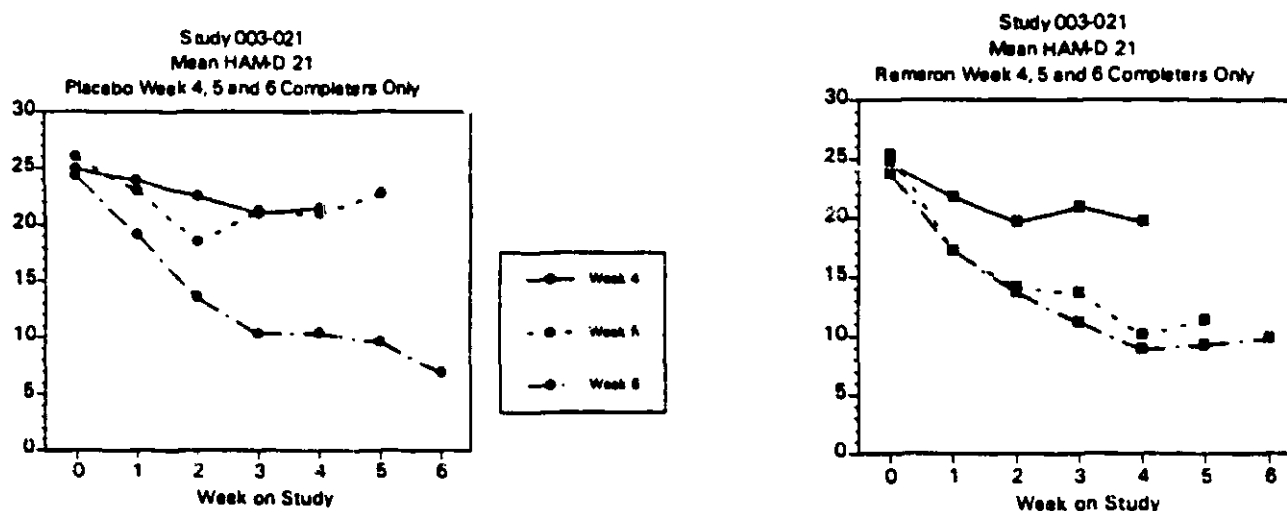


Figure 11

To see if patients reaped some benefit of treatment over time, this reviewer performed 2 repeated measures analyses; one including data from weeks 1-4 and one including data from weeks 1-6 (note that the former analysis includes about 80% of the patients). There is no suggestion that remeron offers any overall benefit over placebo for patients who remain on study at least 4 weeks.

P-values from Repeated Measures Analyses of HAM-D 21 Total

Weeks	REM vs PLA	AMIT vs PLA
1-4	.29	.002
1-6	.55	.32

Table 15 below is designed to compare the results for the remeron-placebo comparisons to the amitriptyline-placebo comparisons. Even in the presence of a large placebo response, amitriptyline shows more significant antidepressant effects than remeron.

Table 15. Study 003-021
Positive Efficacy Results (+ = $p < .05$) By Week

Week	1	2	3	4	5	6
HAM-D 21 Total						
Rem vs Pla						
OC	+	+				
LOCF	+	+		+	+	
Ami vs Pla						
OC	+	+		+		
LOCF	+	+	+	+	+	+
HAM-D #1						
Rem vs Pla						
OC						
LOCF				+		
Ami vs Pla						
OC	+	+	+	+		
LOCF	+	+	+	+	+	+
CGI Severity						
Rem vs Pla						
OC						
LOCF				+	+	
Ami vs Pla						
OC	+			+		
LOCF	+		+	+	+	+
MADRS						
Rem vs Pla						
OC	+					
LOCF	+					
Ami vs Pla						
OC	+			+		
LOCF	+	+		+	+	+

Reviewer's Comment on Study 003-021

The baseline values for Study 003-021 suggest that the population in this study was less sick than patients in the other studies, nevertheless, the magnitudes of the remeron responses are consistent with responses seen in general in this submission. The placebo response (particularly for completers) was larger than expected. Overtime the remeron group rarely is significantly different from placebo (Table 15) and in fact, at Week 6 OC placebo beats remeron (Table 14). On the other hand, the LOCF results for amitriptyline consistently show a significant antidepressant effect over placebo.

This reviewer considers this study to be a negative study for the reasons described in the preceding paragraph (negative efficacy results and positive results for the active control

group). In addition, the large dropout rate (the highest of all the studies) and the large number of LOE dropouts in the remeron group suggest further that this study provides no evidence of efficacy for remeron.

Study 003-022 (Conducted 10/86 to 10/89)

Study 003-022 is a 6-week single center trial. After a one week placebo lead-in, a total of 150 patients were randomized to 3 treatment groups (50 in each group); remeron, placebo and amitriptyline. The treatment groups were balanced at baseline with respect to demographics and disease state. The average age of patients was about 37 years (range of 18 to 93). In the amitriptyline group and the remeron group, about 72% of the patients were female; while in the placebo group, 59% were female. Most of the patients were Caucasian (97%). About 60% of the patients had a baseline diagnosis of recurrent depression. In each treatment group, more than half of the patients reported frequent weeping on the first item of the HAM-D (score of 3); the rest of the patients were evenly split between category 2 (occasional weeping) and category 4 (extreme symptoms). According to the CGI severity score, 13% were moderately ill at baseline; 62% were markedly ill; 21% were severely ill and 3% were among the most extremely ill.

Patient Disposition:

The retention rate for Study 003-022 was high with about 80% of the patients completing the study (Figure 13).

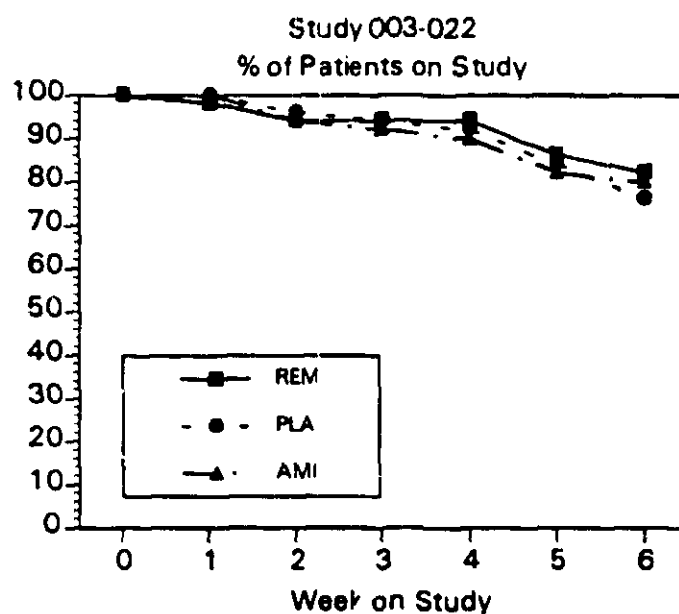


Figure 13

	Randomized	Week 4	Completers
Remeron	50	47 (94%)	41 (82%)
Placebo	50	46 (92%)	38 (76%)
Amitrip.	50	45 (90%)	40 (80%)

As can be seen from Table 16 below, the major reasons for discontinuation from study were lack of efficacy (particularly in the placebo group) and drug-related ADE. All of the placebo LOE dropouts except one discontinued during the last 2 weeks of the study.

Table 16. Study 003-022
Reasons for Discontinuation

REASON	Remeron	Placebo	Amitriptyline
Lack of Efficacy	3 (6%)	9 (18%)	4 (8%)
Drug-related ADE	3 (6%)	0 (0%)	4 (8%)
Non-drug Related ADE	2 (4%)	2 (4%)	2 (4%)
Lost to Follow-up	1 (2%)	0 (0%)	0 (0%)
Patient Improvement	0 (0%)	1 (2%)	0 (0%)

Efficacy Results

The HAM-D 21 Total results over time are depicted below in Figure 14 and Week 6 results are presented in Table 17 on the following page.

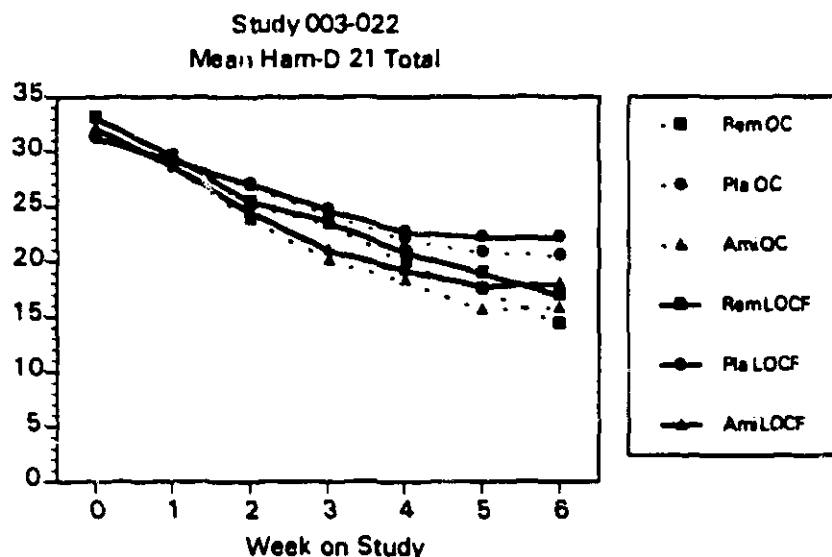


Figure 14

P-values for Comparisons of Change from Baseline By Week

Week	1	2	3	4	5	6
Rem vs PLA ¹						
OC	.07	.007	.16	.08	.03	.003
LOCF	.07	.009	.11	.10	.03	.003
Ami vs PLA						
OC	.02	.0002	.0001	.005	.0004	.005
LOCF	.02	.0005	.0003	.006	.002	.005

¹The treatment groups were different at baseline so this reviewer performed analyses of covariance adjusting for baseline.

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The efficacy results show significant improvement in the remeron group compared to the placebo group on all efficacy measures. Significant differences were observed as early as the first week on study for most of the variables.

Table 17. Study 003-022
Week 6 Efficacy Results for Secondary Endpoints

	Remeron Mean (SD)	Placebo Mean (SD)	P-value Rem vs Pla	Amitriptyline Mean (SD)
Sample Size				
Week 6 OC	37	36		40
Week 6 LOCF	49	50		50
HAM-D 21 Total				
Baseline	33.0 (4.6)	31.2 (4.6)	.06	32.0 (4.7)
Week 6				
OC	-19.4 (9.9)	-11.0 (9.2)	.003*	-16.8 (7.7)
LOCF	-16.1 (10.7)	-9.0 (9.0)	.003*	-14.1 (8.9)
HAM-D Item#1				
Baseline	3.0 (0.6)	2.9 (0.7)	.16	2.8 (0.6)
Week 6				
OC	-2.0 (1.2)	-1.3 (1.2)	.04*	-1.6 (1.0)
LOCF	-1.7 (1.2)	-1.0 (1.2)	.02*	-1.4 (1.0)
CGI-Severity				
Baseline	5.1 (0.7)	5.1 (0.7)	.55	5.2 (0.6)
Week 6				
OC	-2.2 (1.5)	-1.1 (1.3)	.002	-1.8 (1.2)
LOCF	-1.8 (1.6)	-0.8 (1.3)	.003	-1.5 (1.3)
Global Improvement				
Week 6				
OC	2.0 (1.3)	2.9 (1.5)	.002	2.2 (0.9)
LOCF	2.3 (1.4)	3.3 (1.6)	.002	2.4 (1.1)
MADRS				
Baseline	37.7 (5.0)	36.8 (4.8)	.35	36.8 (5.3)
Week 6				
OC	-22.6 (12.8)	-13.4 (11.8)	.005	-19.4 (10.4)
LOCF	-18.7 (13.6)	-11.0 (11.5)	.009	-16.2 (11.5)

*Results of analysis of covariance with baseline as the covariate.

Reviewer's Comments on Study 003-022

It appears that the patient population of Study 003-022 is more severely ill than the patients included in the other 003 studies based on the baseline values of the HAM-D 21 Total, the CGI severity score and the MADRS. Henceforth the magnitude of the responses seen in each treatment group were larger than what was seen in the other studies. Positive results in favor of remeron were observed consistently across the visits and across all efficacy measures. In addition, remeron was significantly superior to placebo for most variables at the first week on study. The results from this study clearly show statistically that remeron is more effective than placebo for the treatment of depression.

Study 003-023 (Conducted 1/87 to 2/90)

Study 003-023 is a 6 week trial which differs in 2 ways from the other 003 studies in this submission; 1) entry criteria specified that patients be over 55 years (the sponsor defined this age group as elderly) and 2) the active control was trazodone (maximum dose allowed of 280 mg).

Fifty (50) patients were randomized to each treatment group (remeron, placebo and trazodone). The mean age of the patients in this study was 62 (range of 55 to 81). Most of the patients were between the ages of 55 and 65; only 30% of the remeron patients, 26% of the placebo patients and 19% of the trazodone patients were 65 or older. (It is worth noting that the FDA guidelines define elderly as 65 years or older.) All but 2 patients were Caucasian. In both control groups, about 60% of the patients were female while in the remeron group 43% were female.

At study entry, 33% of the remeron patients were diagnosed with recurrent depression; while, in the control groups, about half of the patients had this diagnosis. About 3/5's of the patients in each group were described as moderately ill at baseline and reported frequent weeping (a score of 3) on the depressed mood item.

Patient Disposition

From Figure 15, it can be seen that the patient dropout rates in the 3 groups are similar. More than 70% of the patients were able to complete the trial.

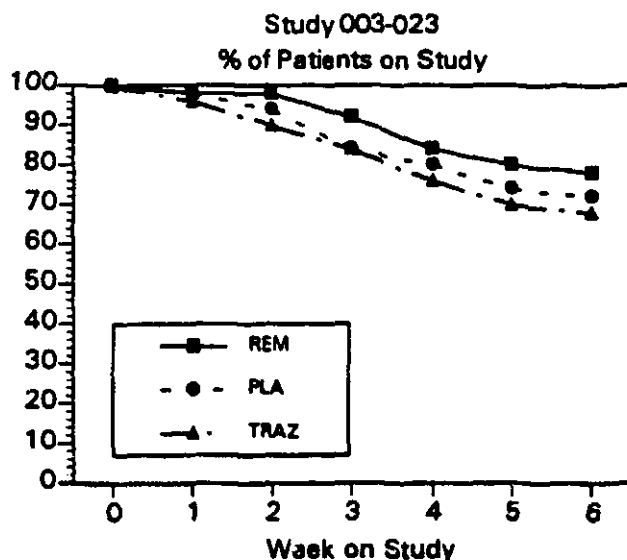


Figure 15

	Randomized	Week 4	Completers
Remeron	50	42 (84%)	39 (78%)
Placebo	50	40 (80%)	36 (72%)
Trazodone	50	38 (76%)	34 (68%)

The reasons for dropout follow a pattern usually seen for antidepressants; the major

reason for dropout in the remeron group is drug related ADE (12%) and the major reason for dropout in the placebo group is lack of efficacy (14%) (Table 18). Four of the 7 placebo LOE dropouts discontinued before completing 3 weeks on therapy. Most of the drug related ADE's in the remeron group occurred during the 3rd week on therapy.

Table 18. Study 003-023
Reasons for Discontinuation

REASON	Remeron	Placebo	Trazodone
Lack of Efficacy	2 (4%)	7 (14%)	6 (12%)
Drug-related ADE	6 (12%)	1 (2%)	5 (10%)
Non-drug Related ADE	0 (0%)	5 (10%)	3 (6%)
Lost to Follow-up	2 (4%)	1 (2%)	0 (0%)
Other	1 (2%)	0 (0%)	2 (4%)

Efficacy Results

The HAM-D 21 Total results are presented below in Figure 16 and in Table

19.

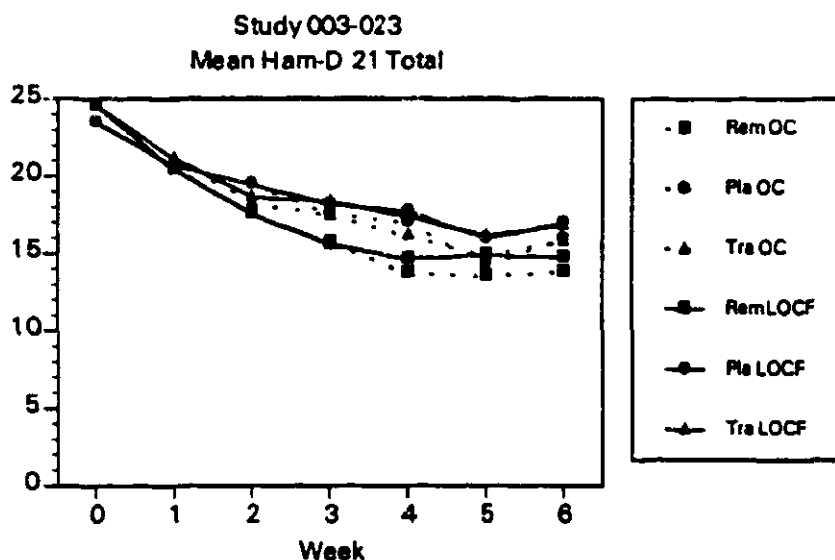


Figure 16

P-values for Comparisons of Change from Baseline By Week¹

Week	1	2	3	4	5	6
Rem vs PLA OC	.15	.007	.08	.007	.33	.05
LOCF	.15	.005	.004	.002	.14	.02
Traz vs PLA OC	.52	.07	.58	.49	.99	.57
LOCF	.52	.13	.49	.43	.66	.44

¹Adjustments for age and baseline did not appreciably change the HAM-D 21 results.

**Table 19. Study 003-023
Week 6 Efficacy Results for Secondary Endpoints**

	Remeron Mean (SD)	Placebo Mean (SD)	P-value Rem vs Pla	Trazodone Mean (SD)
Sample Size				
Week 6 OC	37	34		32
Week 6 LOCF	49	49		48
HAM-D 21 Total				
Baseline	24.6 (4.0)	23.5 (3.1)	.28	24.6 (3.6)
Week 6				
OC	-11.1 (6.5)	-7.6 (7.1)	.05	-8.8 (6.8)
LOCF	-9.9 (6.4)	-6.6 (7.3)	.02	-7.8 (7.1)
HAM-D Item#1				
Baseline	2.6 (0.6)	2.7 (0.5)	.28	2.6 (0.6)
Week 6				
OC	-1.2 (1.1)	-1.0 (1.2)	.35	-0.9 (1.3)
LOCF	-1.0 (1.2)	-0.8 (1.1)	.48	-0.8 (1.3)
CGI-Severity				
Baseline	3.7 (0.6)	3.9 (0.4)	.12	4.0 (0.6)
Week 6				
OC	-1.0 (1.3)	-0.8 (1.2)	.52	-0.8 (1.1)
LOCF	-0.8 (1.3)	-0.6 (1.2)	.36	-0.7 (1.1)
Global Improvement				
Week 6				
OC	2.5 (1.2)	2.7 (1.2)	.44	2.9 (1.2)
LOCF	2.7 (1.2)	3.0 (1.2)	.17	3.1 (1.2)
MADRS				
Baseline	25.3 (6.4)	23.9 (5.6)	.26	26.1 (6.0)
Week 6				
OC	-10.3 (8.6)	-6.8 (9.7)	.14	-10.1 (8.6)
LOCF	-8.8 (9.0)	-5.0 (9.8)	.02	-8.1 (8.4)

The HAM-D 21 Total results suggest some benefit for remeron patients over the placebo patients (Figure 16), however, the results for the secondary variables clearly do not provide supportive evidence for the efficacy of remeron (Table 19). No positive treatment effects were seen at any timepoint (LOCF or OC) for the HAM-D #1, CGI severity score or the global improvement score. For the MADRS score, only the LOCF results were positive at Weeks 2, 3 and 6.

In addition to analyzing the HAM-D 21 Total, the sponsor analyzed the HAM-D 17 Total and 4 factors of the HAM-D (Factors I, III, V and VI). The HAM-D 17 Total results paralleled those seen for the HAM-D 21 Total; the baseline value in each group was about 22 and the endpoint change from baseline for the remeron group was 9.2 compared to a change of 6 for the placebo group. For Factors I (anxiety and somatization) and V (retardation), the sponsor found no treatment differences. For Factors III (cognitive

disturbance) and VI (sleep disturbance), the mean change for remeron was significantly different from placebo at endpoint. However for Factor III, the treatment groups were different at baseline and it appears to this reviewer that an analysis adjusting for baseline would show no difference between the groups on this factor for any of the 6 weeks on drug or at endpoint.

Reviewer's Comments on Study 003-023

The sponsor claims that the lack of efficacy seen in this trial may be due to 2 baseline differences; 1) higher proportion of patients with chronic depression (disease duration > 1 year) in the remeron group than in the placebo group (84% vs 65%, $p = .03$) and 2) higher cognitive disturbance score in the remeron group than in the placebo group at baseline (0.9 vs 0.7, $p = .02$) suggesting (according to the sponsor) more early dementia in the remeron group. This reviewer does not believe there is sufficient evidence showing that these differences affected outcome and the sponsor offered no analyses to support their statements, (for example, an analysis of outcome variables adjusting for duration of disease would have been useful). In light of the fact that the groups did not look different on any other measures at baseline, it seems unlikely to this reviewer that the difference in duration of disease would have an appreciable effect on outcome.

The difference at baseline on the cognitive disturbance score was short-lived since by Week 1 the groups were not different (mean scores for both groups were 0.7). Also significant differences in change from baseline seen at each week would disappear with an analysis adjusting for baseline.

The sponsor's rationale for why trazodone failed to show an effect is that the dose was too low (some studies have shown a dose of 300-400 mg is needed); this appears to be a plausible reason since only 1/3 of the trazodone patients received the maximum dose of 280 mg and the mean overall dose was 151 mg.

The HAM-D 21 Total and MADRS results deserve more detailed inspection. It would be useful to see which items on these scales are changing in order to be able to understand which symptoms of depression remeron is treating in this population of patients over 55 years.

This reviewer concludes that this study was a negative study since it failed to show significant treatment effects on most variables. The lack of a properly dosed active control further clouds the interpretation of this trial as merely a failed study.

Study 003-024 (Conducted 11/86 to 7/88)

Study 003-024 is a single center 6-week trial with 3 treatment arms; remeron, placebo and amitriptyline. After a 7 day placebo lead-in, patients were randomized to each treatment (50 in each group). The mean age of all patients was 42 years (range of 19 to 75). The mean age for the remeron group was larger than the placebo mean (44 years vs 40 years, $p = .07$). About half the patients in the active treatment groups were female while in the placebo group, 67% were female ($p = .2$). 97% of the patients were Caucasian.

The treatment groups were comparable at baseline with regard to severity of disease. About 1/3 of the patients were diagnosed at baseline with recurrent depression. Most patients (68%) reported frequent weeping on the Depressed Mood Item (score of 3). About 58% of the patients were recorded as moderately ill at baseline and 36% were reported as markedly ill.

Patient Disposition

In each treatment group, 50 patients were randomized to treatment. About 90% of the patients completed 4 weeks on study (Figure 17). Most of the dropouts occurred during Week 5. Only 64% of the remeron patients and 54% of the placebo patients completed the study.

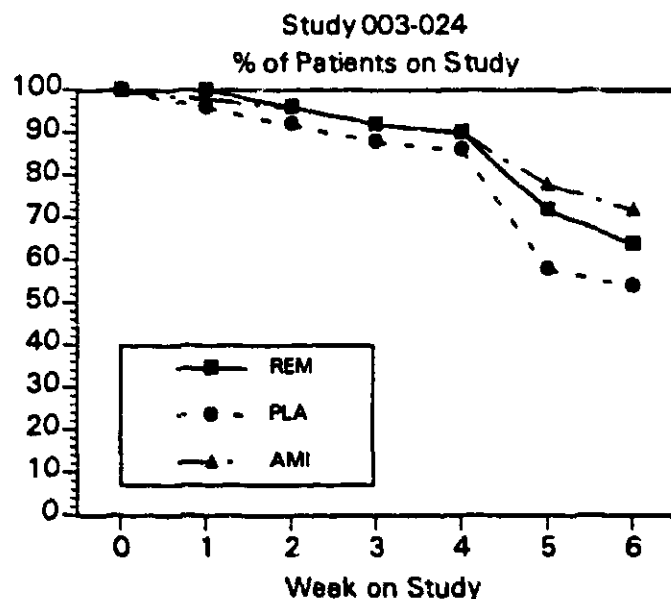


Figure 17

	Randomized	Week 4	Completers
Remeron	50	45 (90%)	32 (64%)
Placebo	50	43 (86%)	27 (54%)
Amitriptyline	50	45 (90%)	36 (72%)

The major reason for dropout in both the remeron and placebo group was lack of efficacy (Table 20 on following page); 8 of the 10 LOE remeron dropouts and 13 of the 16

LOE placebo dropouts occurred during Week 5. About twice as many amitriptyline patients as remeron patients dropped due to drug-related ADE (14% vs 8%). Discontinuations due to ADE's occurred at every week except Week 4.

Table 20. Study 003-024
Reasons for Discontinuation

REASON	Remeron	Placebo	Amitriptyline
Lack of Efficacy	10 (20%)	16 (32%)	4 (8%)
Drug-related ADE	4 (8%)	0 (0%)	7 (14%)
Non-drug Related ADE	1 (2%)	3 (6%)	1 (2%)
Lost to Follow-up	3 (6%)	3 (6%)	1 (2%)
Other	0 (0%)	1 (2%)	1 (2%)

Efficacy Results

The HAM-D 21 Total results are summarized in Figure 18 below. Significant treatment effects were observed at Weeks 2, 4, 5 and 6 LOCF and Week 2 and 4 OC. The Week 6 OC results are borderline significant ($p = .06$).

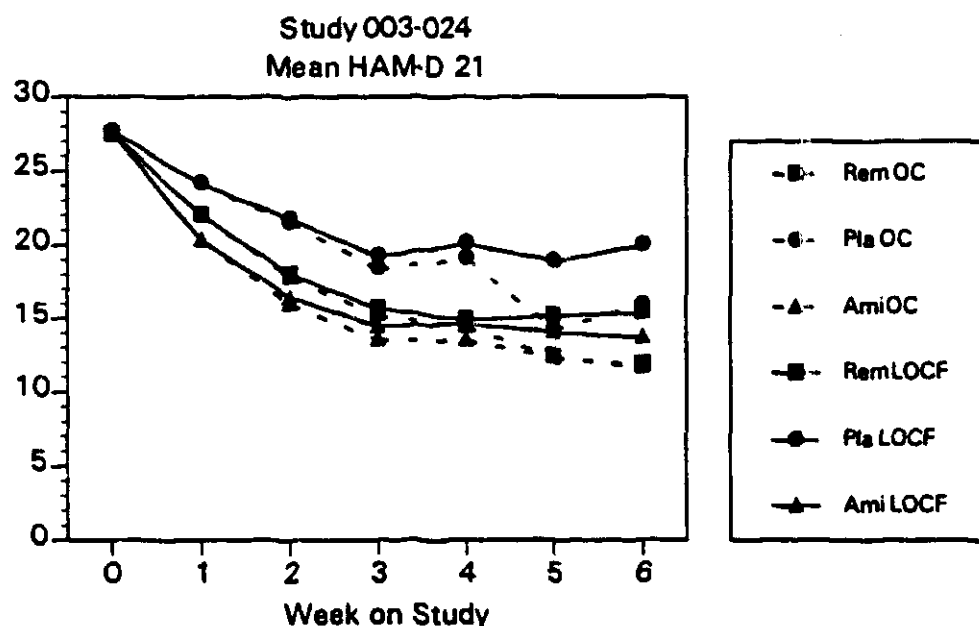


Figure 18

P-values for Comparisons of Change from Baseline By Week

Week	1	2	3	4	5	6
Rem vs PLA OC	.07	.02	.14	.01	.32	.06
LOCF	.07	.02	.08	.004	.05	.01
Ami vs PLA OC	.0008	.001	.007	.002	.30	.03
LOCF	.0008	.001	.007	.002	.01	.0009

Table 21. Study 003-024
Change from Baseline for HAM-D 21 Total at Weeks 4, 5 and 6

	Remeron Mean (SD)	Placebo Mean (SD)	P-value ¹ Rem vs Pla	Amitriptyline Mean (SD)
Baseline	27.5 (3.8) n=50	27.7 (4.4) n=48	.89	27.6 (4.3) n=49
Week 4				
OC	-13.1 (8.5) n=45	-8.4 (8.5) n=43	.01	-14.2 (7.5) n=44
LOCF	-12.6 (8.3) n=50	-7.6 (8.5) n=48	.004	-13.0 (8.6) n=49
Week 5				
OC	-15.3 (6.0) n=36	-13.0 (9.2) n=29	.32 (.24)	-15.5 (6.3) n=39
LOCF	-12.3 (7.9) n=50	-8.8 (9.9) n=48	.05	-13.6 (8.0) n=49
Week 6				
OC	-15.7 (6.7) n=30	-11.1 (9.9) n=27	.06 (.05)	-16.0 (8.0) n=35
LOCF	-12.1 (8.4) n=50	-7.7 (9.7) n=48	.01	-13.9 (9.0) n=49

Focussing on the OC results for the last 3 weeks of the study (Table 21), we see an appreciable jump in the placebo response at Week 5. Figure 19 below illustrates that the placebo response returns to the Week 4 level at Week 6 for the placebo completers. The results of a repeated measures analysis comparing the completers was statistically significant ($p = .02$) suggesting overall benefit due to remeron. Figure 19 also illustrates that the patients completing only 4 weeks of therapy appear to improve (slightly more on remeron than placebo) and then worsen (recall that the primary reason for dropout for these patients was lack of efficacy).

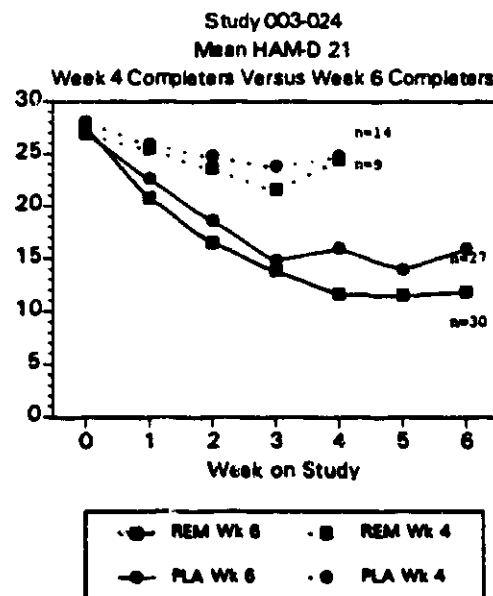


Figure 19

¹A p-value in parentheses is based on an approximate t statistic assuming unequal variances. This statistic was computed when a statistical test revealed that the null hypothesis of equal variances was rejected.

The efficacy results for the secondary variables favor remeron over placebo but not strongly (Table 22). It can be seen for the HAM-D #1 and the CGI-severity score that adjusting for baseline yielded non-significant results. The result over time for these variables show benefit from treatment from Week 3.

Table 22. Study 003-024
Week 6 Efficacy Results for Secondary Endpoints

	Remeron Mean (SD)	Placebo Mean (SD)	P-value ¹ Rem vs Pla	Amitriptyline Mean (SD)
Sample Size				
Week 6 OC	30	27		35
Week 6 LOCF	50	48		49
HAM-D Item#1				
Baseline	2.8 (0.5)	2.7 (0.5)	.13	2.7 (0.6)
Week 6				
OC	-1.4 (1.0)	-0.9 (1.2)	.08 (.16)	-1.5 (1.1)
LOCF	-1.1 (1.1)	-0.6 (1.2)	.02 (.07)	-1.3 (1.1)
CGI-Severity				
Baseline	4.4 (0.5)	4.3 (0.6)	.12	4.5 (0.6)
Week 6				
OC	-1.9 (1.3)	-1.2 (1.6)	.05 (.25)	-2.0 (1.4)
LOCF	-1.4 (1.3)	-0.8 (1.5)	.01 (.07)	-1.7 (1.3)
Global Improvement				
Week 6				
OC	1.9 (0.9)	2.7 (1.4)	.02	1.8 (1.0)
LOCF	2.3 (1.2)	3.2 (1.3)	.001	2.1 (1.3)
MADRS				
Baseline	28.7 (4.6)	27.7 (5.1)	.23	27.9 (5.1)
Week 6				
OC	-15.9 (8.5)	-9.1 (11.8)	.03	-16.8 (8.1)
LOCF	-12.4 (9.3)	-6.2 (10.9)	.002	-15.0 (9.0)

Reviewer's Comments on Study 003-024

Both the LOCF and OC results for the HAM-D 21 Total showed significant treatment effects in spite of the large number of remeron and placebo LOE dropouts (Table 21 and Figure 18). The secondary variables provided supportive evidence of efficacy. This reviewer considers this study to be a positive study illustrating the benefit of remeron over placebo for the treatment of depression.

¹A p-value in parentheses is the result of analysis of covariance adjusting for baseline. It should be noted that tests for equality of variances revealed no significant differences between treatment groups.

Study 003-008 Fixed Dose (Conducted 6/88 to 11/90)

Study 003-008 is a 6-week fixed-dose placebo-controlled single center study. Patients were randomized to one of 5 treatment groups; placebo, 5, 15, 30 and 60 mg/day.

The dosing scheme is shown below. Note that all remeron patients were scheduled to reach their fixed dose no later than the beginning of the third week on treatment.

Titration Scheme by Dose Group and Day on Study

DAY	5 mg	15 mg	30 mg	60 mg
1-2	5 mg	5 mg	5 mg	5 mg
3-4		10 mg	10 mg	10 mg
5-7		15 mg	20 mg	20 mg
8-10	↓		30 mg	30 mg
11-14		↓	↓	45 mg
15-42				60 mg

The 5 treatment groups were comparable with regard to age, gender and race; 66% of the patients were female, 87% were Caucasian and the average age was 40 years (range of 19-70). In addition, the groups were comparable at baseline regarding disease severity according to the HAM-D #1 and the CGI Severity score; about 87% of the patients reported frequent weeping (score of 3 on the Depressed Mood Item) and 72% were recorded as moderately ill. The groups varied in the percentage of patients presenting with recurrent depression as shown in the table below.

% of Patients Diagnosed with Recurrent Depression at Baseline

	Placebo	5 mg	15 mg	30 mg	60 mg
% of Patients	54%	72%	40%	64%	77%

Patient Disposition

A total of 150 were entered into this study; 30 in each treatment group. More patients completed in the placebo group (60%) than in each of the treatment groups ($\leq 50\%$)(Figure 20). The dropout rate in the highest dose group (60 mg) was very high (77%).

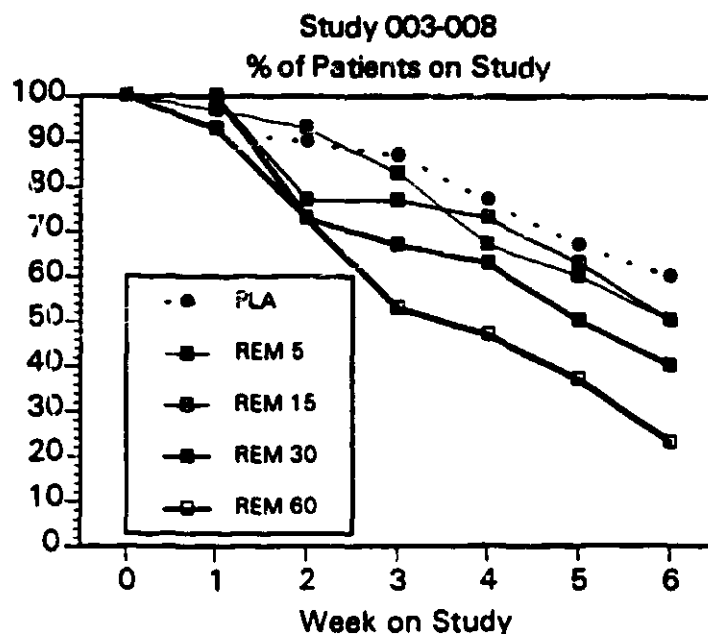


Figure 20

	Randomized	Week 4	Completers
Placebo	30	23 (77%)	18 (60%)
Remeron 5 mg	30	20 (67%)	15 (50%)
Remeron 15 mg	30	22 (73%)	15 (50%)
Remeron 30 mg	30	19 (63%)	12 (40%)
Remeron 60 mg	30	14 (47%)	7 (23%)

The major reasons for dropouts in the remeron groups were LOE and ADE (drug and non-drug related) (Table 23). It is interesting to note that there were more LOE dropouts in the two low dose groups (5 and 15 mg) than in the placebo group. As might be expected, the major reason for dropout in the 60 mg group was ADE (half the randomized patients). Most of the ADE dropouts occurred during Weeks 2 and 3 (recall that patients reached their maximum dose by the end of Week 2). LOE dropouts occurred steadily throughout the trial.

Table 23 Study 003-008
Reasons for Discontinuation

REASON	Placebo	5 mg	15 mg	30 mg	60 mg
Lack of Efficacy	6 (20%)	9 (30%)	8 (27%)	5 (17%)	4 (13%)
Drug-related ADE	1 (3%)	4 (13%)	4 (13%)	7 (23%)	9 (30%)
Non-drug Related ADE	3 (10%)	2 (7%)	3 (10%)	5 (17%)	6 (20%)
Lost to Follow-up	2 (7%)	0 (0%)	0 (0%)	0 (0%)	3 (10%)
Other	0 (0%)	0 (0%)	0 (0%)	1 (3%)	1 (3%)

Efficacy Results

The sponsor's pairwise comparisons of each dose to placebo revealed no significant treatment differences on the HAM-D 21 Total (LOCF and OC). The LOCF results are depicted below in Figure 21. Minimal differences in favor of remeron ($p < .10$) were noted after one week on study but no significant differences were observed for the remaining 5 weeks of the trial ($p > .2$, most p-values were greater than .5).

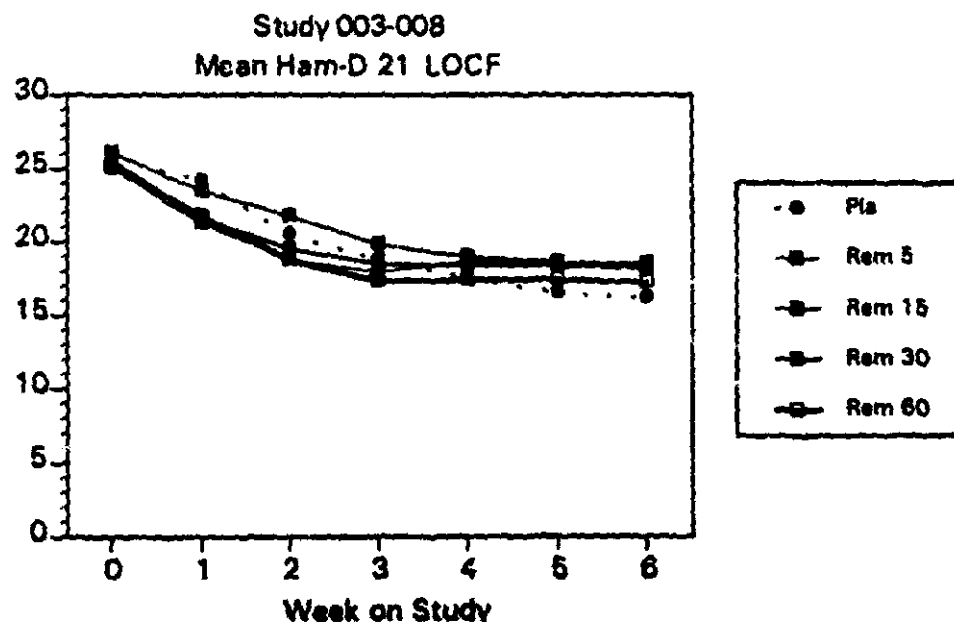


Figure 21

A plot of the completer data suggests that patients who complete the study in the remeron 60 mg group benefit from treatment. However, since only 7 patients completed the study on 60 mg, the sample size is too small to discern a statistically significant difference from placebo.

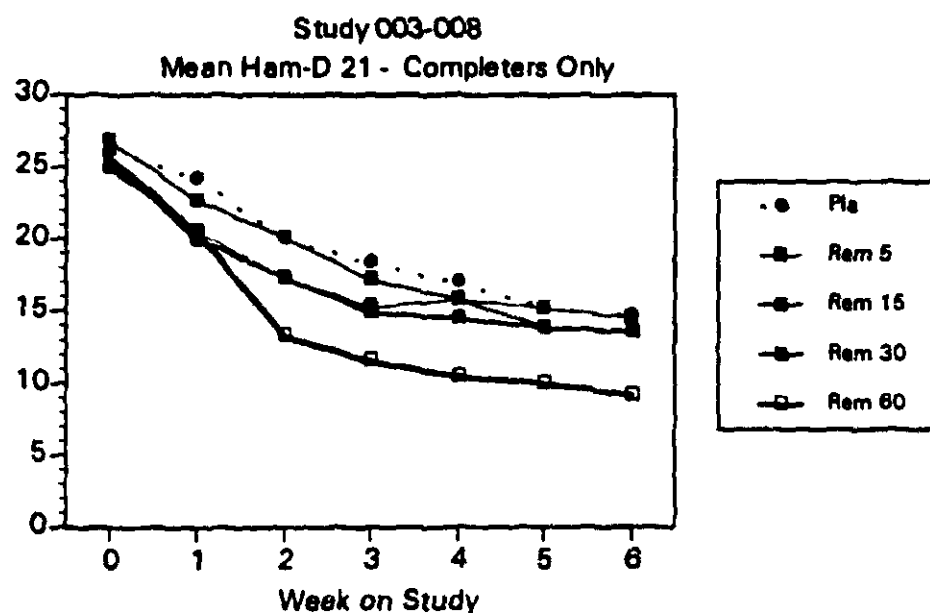


Figure 22

The table below presents the mean changes at Week 6 for all the efficacy variables. As for the HAM-D 21 Total, no dose of remeron was significantly different from placebo for any secondary variables.

Table 24. Study 003-008
Efficacy Results
Mean Changes

	PLA	REM 5	REM 15	REM 30	REM 60
HAM-D 21 Total					
Baseline	25.8	25.0	26.0	25.5	25.3
Week 6					
OC	-11.4	-10.5	-13.2	-11.9	-16.6
LOCF	-9.6	-8.8	-7.6	-6.8	-8.1
HAM-D Item #1					
Baseline	2.9	2.8	3.0	2.9	2.9
Week 6					
OC	-1.2	-0.9	-1.3	-1.3	-1.6
LOCF	-0.9	-0.6	-0.8	-0.6	-0.7
CGI-Severity					
Baseline	4.3	4.2	4.3	4.3	4.2
Week 6					
OC	-1.5	-1.3	-1.7	-1.7	-2.1
LOCF	-1.1	-0.8	-0.8	-0.8	-0.9
Global Improvement					
Week 6					
OC	2.2	2.3	1.8	1.9	1.4
LOCF	2.6	3.0	2.8	3.0	2.7
MADRS					
Baseline	27.6	27.0	28.2	27.3	27.9
Week 6					
OC	-10.4	-9.9	-13.5	-10.5	-13.8
LOCF	-8.3	-6.2	-7.2	-6.2	-7.3

To determine if there is a relationship between dose and response (excluding placebo) this reviewer performed a Jonckheere-Terpstra test on the Week 6 data (LOCF and OC) and found no significant trends ($p > .15$).

Reviewer's Comments on Study 003-008

Analyses performed by the sponsor (pairwise comparisons) and by this reviewer (dose response tests) revealed no statistically significant treatment effects. This study was marred by large dropout rates in the remeron groups ($\geq 50\%$); a total of 150 patients were randomized and only 67 patients completed 6 weeks. About 1/5 of the patients discontinued due to lack of efficacy (see Table 19); this may be due to the fact that this was a fixed dose study and so patients/investigators dissatisfied with their response did not have the option to increase the dose.

In conclusion, the results of this study do not provide evidence for the efficacy of remeron for the treatment of depression.

Foreign Studies 84023 and 85027

Common Design Features of Studies 84023 and 85027

Studies 84023 and 85027 were both multicenter studies. Patients with a primary diagnosis of major depressive episode (predominantly endogenous depression based the Newcastle Endogenous/Reactive Depression Rating Scale screening at baseline) were randomized to remeron or placebo after a 1-week placebo washout. To be eligible for randomization, patients needed a score of 18 or greater on the HAM-D 21 Total and less than a 25% drop on the HAM-D 21 after the washout period.

The efficacy variables in both trials were; HAM-D 21 Total, MADRS, Brief Psychiatric Rating Scale (BPRS) and the Global Assessment Score (GAS). The GAS is measured on a scale of 1 to 100 where 1 = severe dysfunction and 100 = no symptoms, superior function. Results for all variables except the BPRS will be summarized here. In addition, FDA requested that the sponsor analyze the HAM-D Depressed Mood Item (item #1).

Study 84023

Study 84023 is the only controlled study in the NDA submission of hospitalized patients. A total of 117 inpatients were randomized to placebo or remeron at 8 centers in Finland. During this 6-week trial, patients could be titrated to the maximum doses shown in the table below.

Week on Study	Max Dose Allowed
1	15 mg
2	25 mg
3	35 mg
4-6	50 mg

There were slightly more females in the remeron group than the placebo group (58% vs 49%). The average age of all the patients was 46 years (range of 16 to 83). (Information about race was not presented in the submission.)

The groups were comparable at baseline on measures of severity of illness (also the values were consistent with what was observed in the studies of outpatients). About 2/3's of the patients reported frequent weeping at baseline (HAM-D #1, score of 3).

Patient Disposition¹

A total of 117 patients were randomized to treatment (60 to remeron and 57 to placebo); 3 patients never received any treatment. Six of the 8 centers recruited 7 to 14 patients in each treatment group; 1 center recruited only 6 patients and a second center only 3 patients.

From the figure below, we see that most of the dropouts occurred during weeks 3 and 4. 62% of the remeron and 54% of the placebo patients were able to complete the study.

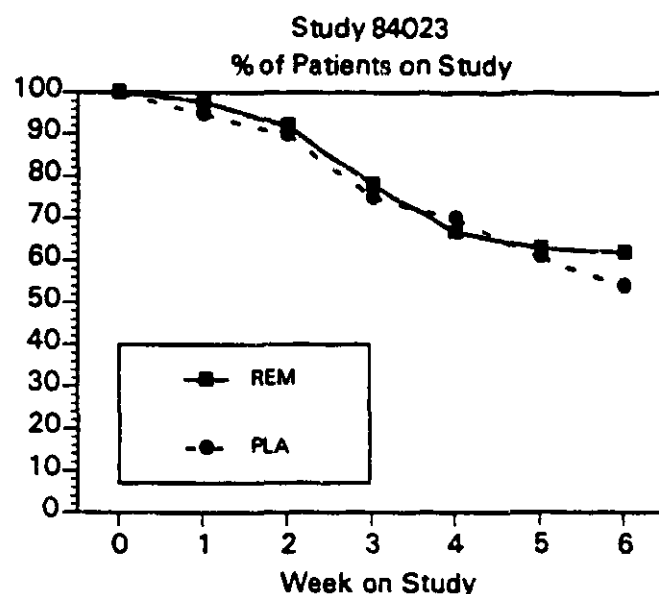


Figure 23

	Randomized	Week 4	Completers
Remeron	60	40 (67%)	37 (62%)
Placebo	57	40 (70%)	31 (54%)

The primary reason for dropout in both groups was lack of efficacy (see Table 25 on the following page) with 20% of the remeron patients and 28% of the placebo patients dropping for this reason. Non-compliance was high in both groups however the patient listings suggests that some of these patients were non-compliant due to lack of efficacy. (The number of non-compliant patients seems high given this study was conducted in hospital.)

¹ The data on patient disposition comes from 3 sources; the sponsors first and second submissions and the database. None of these sources agreed precisely. Patient listings from the submission were used along with the database to interpret the summary data presented by the sponsor and to obtain an accurate count for this review.

**Table 25. Study 84023
Reasons for Discontinuation**

REASON	Remeron	Placebo
Lack of Efficacy	12 (20%)	16 (28%)
ADE	1 (2%)	0 (0%)
Non-drug Related Reason	2 (3%)	5 (9%)
Patient Improvement	2 (3%)	0 (0%)
Non-compliance	4 (7%)	5 (9%)
Suicide	2 (3%)	0 (0%)

Efficacy Results

The efficacy results are summarized below for Week 6. The HAM-D was administered at baseline and at the time of dropout or at the end of the trial; the MADRS at Weeks 2, 4 and 6 and the GAS weekly.

**Table 26. Study 84023
Week 6 Efficacy Results**

	Remeron Mean (SD) N	Placebo Mean (SD) N	P-value Rem vs Pla
HAM-D 21 Total			
Baseline	25.6 (4.3) 45 ¹	26.0 (4.6) 45	.55
Week 6			
OC	-14.2 (7.8) 35	-11.9 (8.6) 33	.25
LOCF	-10.9 (9.7) 44	-9.0 (9.2) 45	.38
HAM-D Item#1			
Baseline	2.9 (0.7) 44	2.8 (0.7) 45	.38
Week 6			
OC	-1.4 (1.0) 35	-1.1 (1.2) 33	.32
LOCF	-1.0 (1.3) 44	-0.8 (1.1) 45	.53
GAS			
Baseline	41.3 (8.9) 59	40.8 (8.1) 52	.77
Week 6			
OC	+22.0 (13.9) 37	+19.3 (13.2) 30	.39
LOCF	+16.1 (14.5) 59	+13.4 (15.3) 52	.40
MADRS			
Baseline	32.4 (6.4) 54	33.0 (5.9) 52	.70
Week 6			
OC	-16.6 (12.3) 36	-15.3 (12.7) 32	.90
LOCF	-13.1 (12.0) 54	-9.6 (13.4) 52	.17

¹ The summary tables presented in the sponsor's original submission show that 59 remeron patients and 55 placebo patients had baseline data for the HAM-D however not all this data was included in the database provided to this reviewer.

These results show no statistically significant treatment effects. The sponsor also analyzed the factors of the HAM-D and found no significant treatment effects for any of the factors.

To see if the data collected over time suggested any benefit for the remeron patients over the placebo patients, this reviewer performed a repeated measures analysis of the MADRS. The results were negative ($p > .70$), however it should be pointed out that the analysis includes only about half the patients (only patients with non-missing data). The graph of the observed case data and the LOCF data shown below suggests also only a minimal treatment effect exists particularly when one adjusts for the small baseline difference.

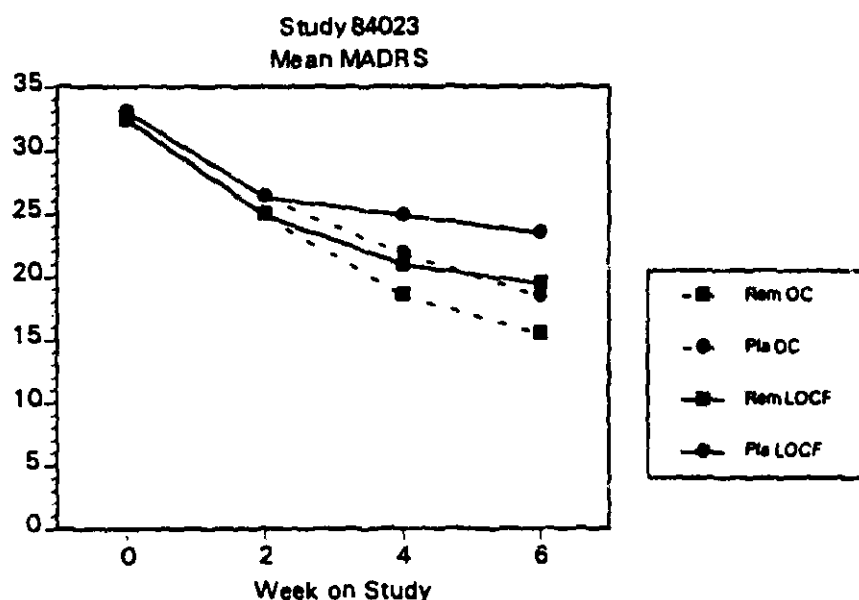


Figure 24

Reviewer's Comments on Study 84023

The results of this study do not suggest any benefit from remeron treatment in a population of hospitalized patients. The most disconcerting results of this study were the number of suicides (2 in the remeron group) and the high number of discontinuations in the remeron group due to lack of efficacy (Table 25).

Study 85027

Study 85027 is a 5-week dose-titration placebo-controlled study conducted in England at 3 centers. The protocol allowed for the inclusion of inpatients but from the study reports it appears that only outpatients were recruited.

During this 5-week trial, patients could be titrated to the maximum doses shown in the table below. Dosing was BID; when equal dosing was not possible, the higher dose was given in the evening.

Week on Study	Max Dose Allowed
1	20 mg
2	30 mg
3	40 mg
4-5	60 mg

About ⅔'s of the patients were female. The average age was about 41 years (range of 18 to 64). (No information regarding race was provided.)

Patient Disposition

A total of 130 patients were randomized to treatment; 64 to remeron and 66 to placebo. The completion rates were high in this 5-week study with about 78% of the patients completing in each group.

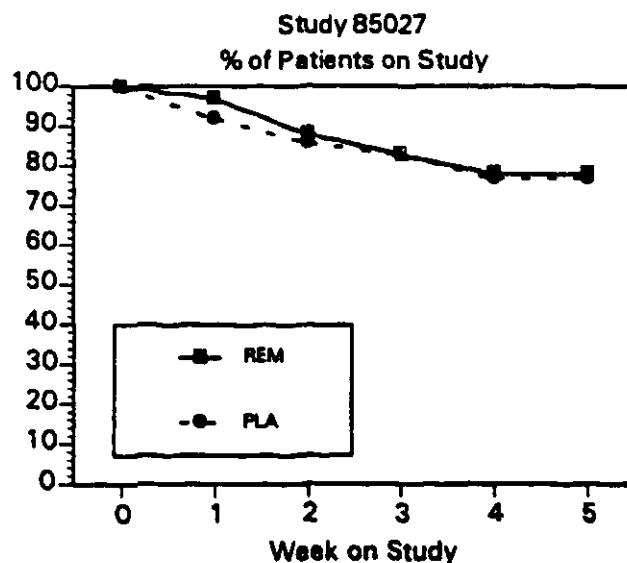


Figure 25

	Randomized	Week 4	Completers
Remeron	64	50 (78%)	50 (78%)
Placebo	66	51 (77%)	51 (77%)

The major reason for discontinuation in both groups was lack of efficacy; most of those occurred during the second and third week on study. Four of the 5 ADE's observed in the remeron group occurred during Week 2.

Table 27. Study 85027
Reasons for Discontinuation

REASON	Remeron	Placebo
Lack of Efficacy	6 (8%)	8 (12%)
ADE	5 (8%)	1 (2%)
Non-drug Related Reason	2 (3%)	1 (2%)
Patient Improvement	1 (2%)	2 (3%)
Non-compliance	1 (2%)	4 (6%)

Efficacy Results

The HAM-D and the MADRS were assessed at Weeks 2, 4 and 5. According to the protocol the MADRS was considered the primary outcome measure. The GAS was administered weekly. The results at Week 4 show a significant treatment effect whereas the Week 5 results are not significant (Figure 26). Since no patients dropped out during Week 4, the results show that the placebo patients improved while no change was seen for the remeron patients. A repeated measures analysis of Weeks 2, 4 and 5 revealed a significant treatment effect ($p = .03$).

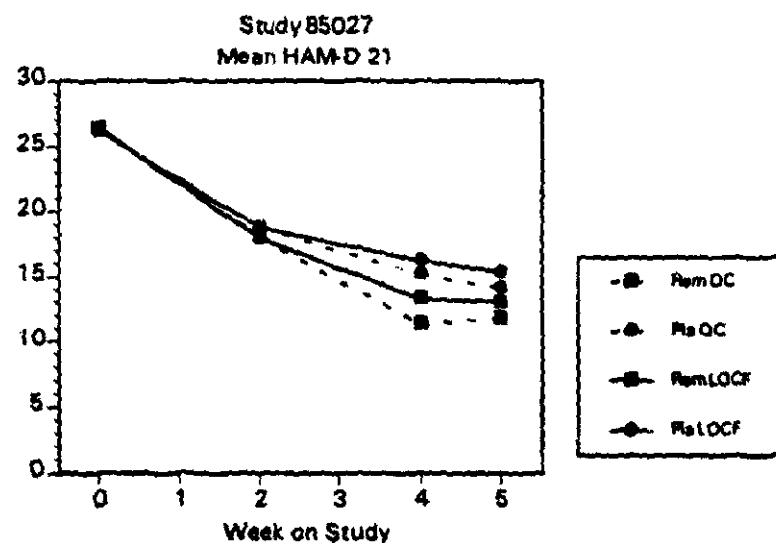


Figure 26

P-values from Comparisons of Change from Baseline by Week

Week	2	4	5
Rem vs PLA			
OC	.87	.006	.10
LOCF	.87	.07	.19

The efficacy results for the HAM-D #1, the GAS and the MADRS at Week 5 favor remeron; the GAS results are borderline significant (Table 28).

**Table 28. Study 85027
Week 5 Efficacy Results**

	Remeron Mean (SD) N	Placebo Mean (SD) N	P-value Rem vs Pla
HAM-D 21 Total			
Baseline	26.4 (3.7) 64	26.2 (5.0) 61	.57
Week 5			
OC	-14.7 (8.4) 51	-11.8 (8.3) 48	.10
LOCF	-13.4 (8.6) 64	-10.9 (8.9) 61	.19
HAM-D Item#1			
Baseline	2.3 (0.5) 64	2.2 (0.6) 61	.15
Week 5			
OC	-1.3 (1.0) 51	-0.8 (0.9) 48	.01
LOCF	-1.2 (0.9) 64	-0.8 (0.9) 61	.03
GAS			
Baseline	50.1 (6.9) 64	50.9 (7.2) 66	.45
Week 5			
OC	+ 23.8 (16.8) 51	+ 17.5 (15.7) 48	.07
LOCF	+ 20.9 (17.3) 64	+ 15.2 (15.7) 66	.06
MADRS			
Baseline	29.4 (5.6) 64	28.4 (6.2) 61	.23
Week 5			
OC	-17.5 (10.0) 51	-12.5 (9.5) 48	.02
LOCF	-15.7 (10.1) 64	-11.6 (9.6) 61	.04

Reviewer's Comments on Study 85027

The baseline values for this study suggest a less sick population than what was observed in the other studies.

The results for both the HAM-D 21 and the GAS were close to significance while the HAM-D depressed mood item and MADRS results both showed significant treatment effects at Week 5 (LOCF and OC).

The results from this study are supportive but weak due to the lack of efficacy on the HAM-D 21 Total at Week 5. Also, as in many of the studies of this submission, the major reason for dropout in the remeron group was lack of efficacy.

Dosing

The table below summarizes the dosing data for the flexible dose studies in this submission. With the exception of patients in Studies 003-022 and 003-023, more than 2/3's of the patients did not take the maximum dose allowed. Of the 003 studies where a maximum dose of 35 mg was allowed, Study 003-022 used the highest doses. This may be related to the fact that the patients in this study appeared to be more severely ill at entry according to their baseline efficacy values compared to patients in many of the other studies.

Table 29. Dosing Data for Flexible Dose Studies

Study	Overall Mean Dose (mg/day)		Mean of Modal Dose (mg/day)		% of Patients Taking Max Dose Allowed ¹	
	REM	PLA	REM	PLA	REM	PLA
003-002	16.6	20.5	18.8	20.0	18%	57%
003-003	19.9	22.0	20.3	22.5	29%	38%
003-020	14.4	16.5	18.2	20.5	17%	38%
003-021	17.0	17.5	21.1	22.5	24%	19%
003-022	22.0	24.5	26.0	30.0	67%	84%
003-023	20.1	20.5	24.5	25.0	51%	49%
003-024	16.0	19.5	18.0	23.0	22%	50%
84023	24.2	NA	NA	NA	14% ²	16%
85027	36.0	NA	NA	NA	50% ³	53%

In four studies, the active control drug was amitriptyline. The maximum dose allowed of amitriptyline was 240 mg per day. In Study 003-022, 38% of the amitriptyline patients were titrated to the maximum dose while in the other studies less than 15% did so. The overall mean dose of amitriptyline in Studies 003-020 and 003-021 was 93 mg; in 003-022, 133 mg and in 003-024, 108 mg.

¹ These numbers generally matched the percentages of patients taking the maximum dose as the final dose. For the 003 studies, the maximum dose allowed was 35 mg/day, for Study 84023, the maximum dose allowed was 50 mg/day and for Study 85027, the maximum dose allowed was 60 mg/day.

² 42% of the remeron patients had a maximum dose of 35 mg or greater.

³ 97% of the remeron patients had a maximum dose of 30 mg or greater; 81% had a max of 40 mg or greater.

Long Term Extension Trials

Six of the studies conducted by the sponsor had long-term double-blind extensions. These studies are summarized in Table 30 below. (Note that all the information presented in this section of the review is from the sponsor's study report. The data for these studies was not requested by this reviewer.)

For Studies 003-004 and 003-005, patients were continued on the same medication at the same dosing level that they had received during the short-term segment of the study. The patient numbers for Studies 003-004 and 003-005 are too small (about 10% of the patients randomized in the short-term segments of the studies continued into long-term treatment) to provide sufficient evidence of long-term efficacy.

Table 30. Long term Extension Studies

Short-term Study	Long-term Extension	Length of Extension	# of Patients	HAM-D 17 Total			Mean of Modal Dose ¹
				Baseline	ST Endpoint	LT Endpoint	
003-002	003-004	7 Weeks	8 Remeron 2 Placebo	REM 21.9 PLA 24.0	5.3 3.0	6.2 3.0	16.3 mg
003-003	003-005	7 Weeks	10 Remeron 4 Placebo	REM 23.0 PLA 20.8	7.3 5.0	7.4 5.5	24 mg
003-020	003-025	20 Weeks + 24 week extensions	33 Remeron 18 Amitrip. 11 Placebo	The sponsor pooled the 4 studies and summarized data for switchers and non-switchers separately. <u>NON-SWITCHERS</u> REM (n=72) 24.5 7.4 4.8 PLA (n=54) 23.5 8.9 9.5 AMI (n=82) 24.1 7.7 7.5 <u>SWITCHERS</u> PLA/REM (n=74) 24.2 22.8 11.9 AMI/REM (n=49) 26.0 18.2 10.0 REM/AMI (n=57) 24.1 18.9 16.0			No data on dosing was provided in the study report.
003-021	003-026	20 Weeks + 24 week extensions	40 Remeron 47 Amitrip. 19 Placebo				
003-022	003-027	20 Weeks + 24 week extensions	74 Remeron 40 Amitrip. 17 Placebo				
003-024	003-028	20 Weeks + 24 week extensions	54 Remeron 40 Amitrip. 10 Placebo				

Patients in the long-term segments of the 4 003-02x studies were assigned treatment according to the discretion of the investigator, so patients could remain on their randomized treatment or be switched to a different active treatment group (remeron or amitriptyline). Therefore, the treatment groups in the long-term extension are not randomized groups precluding the use of statistical tests to make comparisons. Descriptive statistics suggest continued improvement is seen with long-term use of remeron for this selected group of patients (Table 30)

¹Computed from data for the short and long-term segments combined.

Table 31 below presents the number of patients on study for the 4 studies pooled together. About half the patients completed the first 20-week extension. The major reasons for patient discontinuation among the non-switchers and the patients switching to remeron were patient improvement and non-drug related reasons. The major reason for discontinuation in the patients who switched from remeron to amitriptyline was drug-related ADE. Very few patients in any group dropped due to lack of efficacy.

Table 31. Patient Disposition in Studies 003-025, 003-026, 003-027 and 003-028 Combined

	Non-Switchers			Switchers		
	REM	PLA	AMI	PLA/REM	AMI/REM	REM/AMI
N(%) at Start of Extension	72 (100%)	54 (100%)	82 (100%)	74 (100%)	49 (100%)	57 (100%)
Week 20	46 (64%)	30 (56%)	49 (60%)	43 (58%)	23 (47%)	24 (42%)
Week 44	18 (25%)	5 (9%)	15 (18%)	17 (23%)	8 (16%)	4 (7%)
Week 68	8 (11%)	3 (6%)	12 (15%)	11 (15%)	5 (7%)	2 (4%)
Week 92	2 (3%)	1 (2%)	2 (2%)	3 (4%)	1 (2%)	1 (2%)
Week 116	0	0	1 (1%)	1 (1%)	1 (2%)	0

Summary and Conclusions

The focus of this review has been 10 studies submitted by the sponsor. These 10 studies consist of 7 USA titration studies (003 studies 002, 003, 020, 021, 022, 023 and 024), 1 USA fixed-dose study (003-008) (these 8 are listed in Table 2) and 2 foreign studies (listed in Table 3). To summarize the results for this NDA, this reviewer has combined the data from the 7 titration studies. The designs for these 7 studies were very similar; they were all 6 week placebo-controlled single-center studies where the maximum dose allowed was 35 mg. Four of the 7 studies had a third treatment group; amitriptyline in 3 and trazodone in 1. The patient populations were similar in these trials with the exception of 003-023 where patients needed to be 55 or older. (Analyses done by this reviewer indicated that the responses of older patients were consistent with the responses of younger patients so Study 003-023 was included in the pooled dataset.) Studies 003-008, 84023 and 84027 are not included in the summary that follows but are included in the final summary table. These studies were reviewed in detail but are excluded here because their designs differ considerably from the 003 titration studies (for details see the review of each study) and, also, none of these 3 trials were positive trials for remeron.

Patient Population

A total of 833 patients were enrolled in the 7 003 titration trials; 323 patients were randomized to remeron, 323 to placebo and 187 to amitriptyline (see Table 2 for numbers of patients in each trial). There were slightly more females (56%) than males enrolled in these trials. Almost all (95%) of the patients were Caucasian. The mean age of the patients was 45 years (range of 18 to 93) with about half the patients between the ages of 35 and 56.

The mean baseline efficacy values (Table 32 below) were comparable across the treatment groups. (Note that the amitriptyline means appear to be slightly higher but in the 3 studies with amitriptyline as an active control the means were comparable to the other groups.)

Table 32. Mean Baseline Values for Efficacy Variables
All 003 Studies Combined

	Remeron (N = 323)	Placebo (N = 323)	Amitriptyline (N = 187)
Baseline HAM-D 21	26.7 (5.1)	26.6 (5.1)	28.4 (5.6)
Baseline HAM-D Item #1	2.7 (0.6)	2.7 (0.6)	2.7 (0.6)
Baseline CGI Severity Score	4.3 (0.6)	4.4 (0.7)	4.7 (0.7)
Baseline MADRS	29.1 (6.6)	29.5 (6.6)	30.7 (6.9)

At baseline about 60% of the patients reported frequent weeping on the Depressed Mood Item of the HAM-D (score of 3); another 30% reported occasional weeping (score of 2) while only about 5% reported extreme symptoms of sadness (score of 4). Most of the patients were diagnosed as moderately ill at baseline (about 60%), 30% markedly ill and 6% severely ill.

Efficacy Results

Efficacy Responses at Week 6

The mean results for the HAM-D 21 Total at Week 6 (OC and LOCF) for each of the 003 studies are summarized in the graphs and table below.

The results for 2 of the studies (003 and 021) clearly do not favor remeron over placebo so this reviewer considered both of these studies to be negative studies (note that amitriptyline beats placebo at Week 6 LOCF in Study 021). The placebo response is large in both studies, however these responses are consistent with the level of response observed in some of the positive studies (for example, the placebo response for Study 003 is comparable to the response in Study 002 for OC and Study 022 for LOCF).

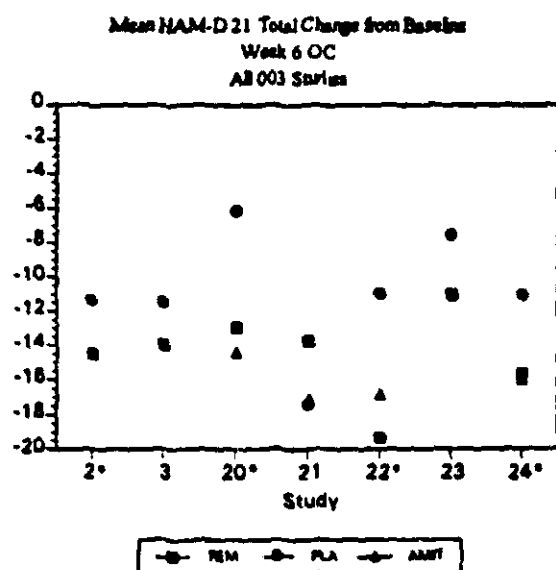


Figure 27

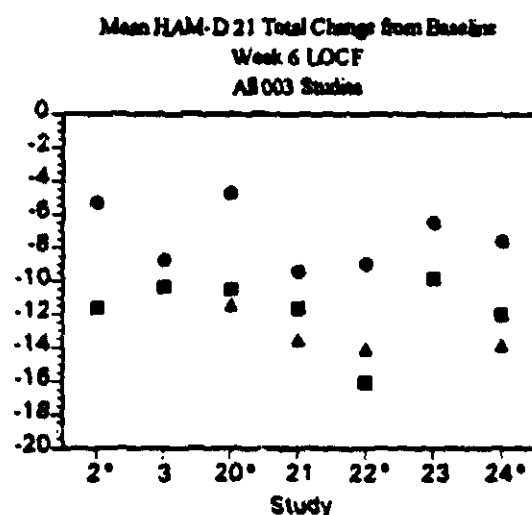


Figure 28

Week 6 HAM-D 21 Total Results by Study							
P-values for Comparisons of Change from Baseline							
Study	002	003	020	021	022	023	024
REM vs PLA							
OC	.30	.51	.007	.06 ¹	.003	.05	.06 ²
LOCF	.0008	.49	.04	.22	.003	.02	.01
AMIT vs PLA							
OC	NA	NA	.002	.93	.005	NA	.03
LOCF			.0009	.02	.005		.0009

¹ Results favor placebo.

² An analysis accounting for unequal variances yielded a p-value of .05.

For 4 of the 7 studies (020, 022, 023 and 024), remeron was statistically significantly different from placebo at Week 6 for both the LOCF and OC datasets. This reviewer considered Studies 020, 022 and 024 to be positive studies. Study 023 showed some positive results on the HAM-D 21 and the MADRS but not on the HAM-D #1, the CGI severity score or the Global so this reviewer considered the results to be negative.

In Study 002, the LOCF results were statistically significant while the OC results were not. This reviewer considered this to be a positive study because the LOCF results were positive at every week and the major reason for the nonsignificant OC results was the large number of placebo dropouts at Week 5 and 6 due to LOE (see the review of this study on pages 5 to 9 for more details).

So the statistical evidence suggests that 4 studies are positive studies and 3 are negative. In addition, recall that the dose-response study (003-008) and the 2 foreign studies failed to provide definitive evidence of efficacy for remeron over placebo.

Efficacy Responses Over Time

The full 6 weeks of efficacy results for some of the studies suggest that patients respond early to remeron. In 2 studies (002 and 022), a significant treatment group effect on both the HAM-D 21 Total and the HAM-D Depressed Mood Item was observed at Week 1 and sustained for the duration of the trial. To examine this issue, this reviewer identified protocol-defined responders (patients with a 50% or greater drop on the HAM-D 21) at each week in the seven 003 studies combined (Figure 29 below). Patients with no data were counted as non-responders so the denominator was the same at each week. (A graph of just the 4 studies with amitriptyline as a control was nearly identical to the one below.) There is no suggestion that remeron patients respond faster than amitriptyline patients. Also note that the treatment difference at Week 1 is small (less than 5%). At Week 2, there are approximately twice as many remeron responders as placebo responders; this difference dwindles over the last 4 weeks.

Percentage of Patients with 50% Change or Greater on
the HAM-D 21 Total
All Dropouts Defined as Non-responders
003 Studies Combined

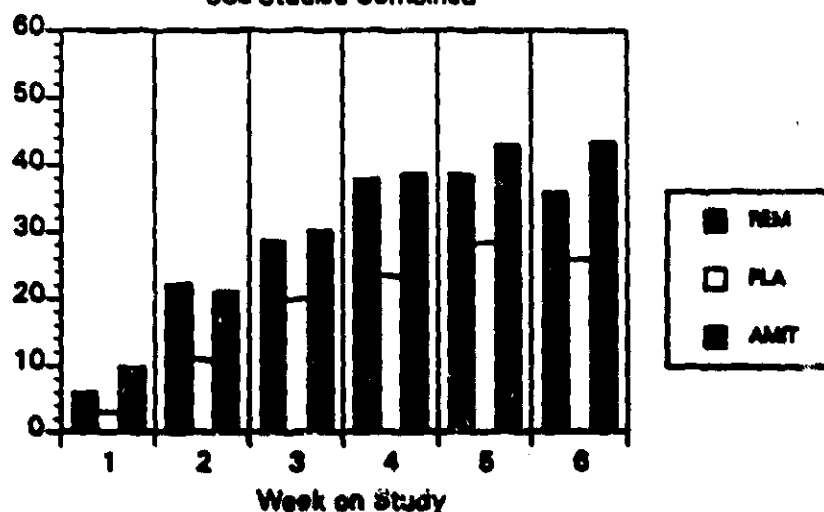


Figure 29

The graphs below depict the mean for the HAM-D 21 Total and for the HAM-D Depressed Mood Item over the duration of the trials. Most of the effect occurs during the first 3 weeks of the study (a drop of about 10 on the HAM-D Total). LOE dropouts in the placebo group typically occurred during Week 5 in these trials leading to the differences between the OC and LOCF responses at Weeks 5 and 6 for the placebo patients observed in most of the studies and resulting in small usually nonsignificant treatment differences at the last 2 weeks of the study.

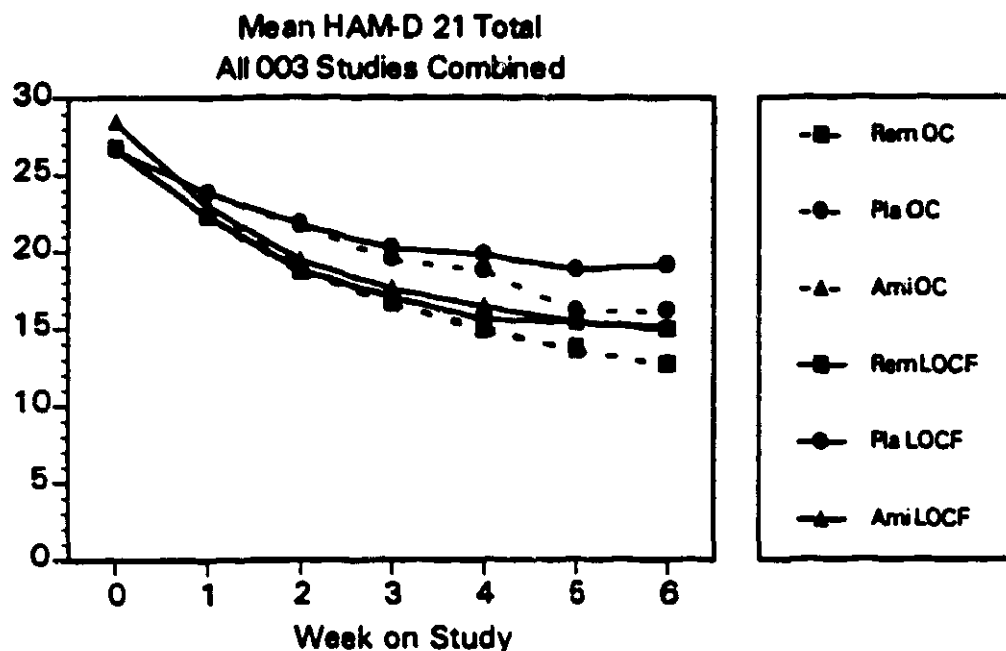


Figure 30

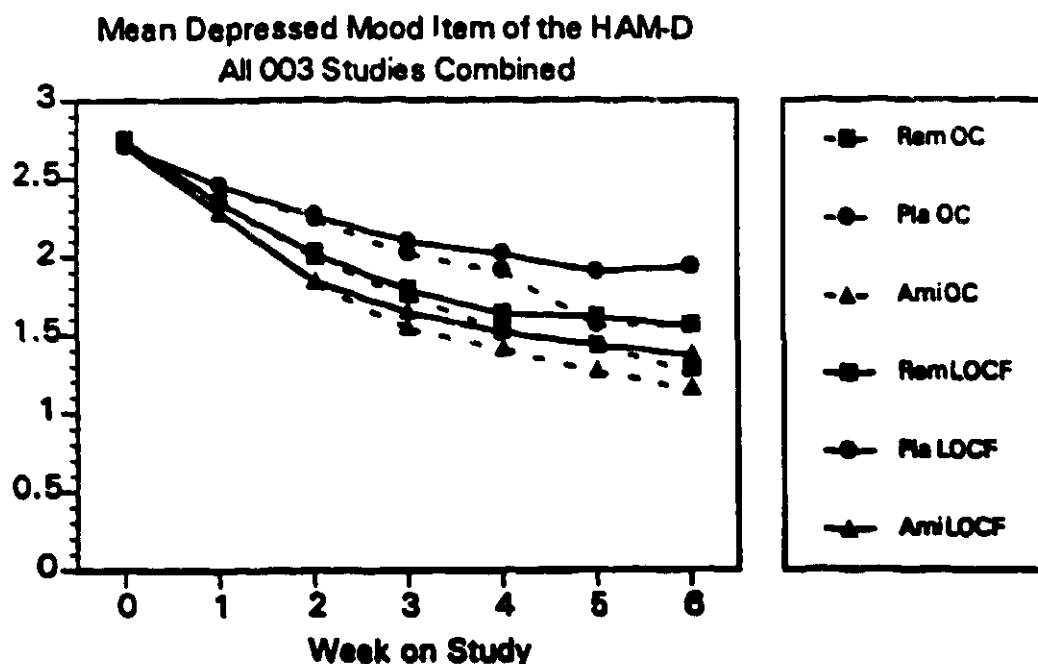


Figure 31

In addition to looking at the HAM-D 21 Total and the first item of the HAM-D, the sponsor analyzed 4 factors of the HAM-D; Factor I (anxiety/somatization), Factor III (cognitive disturbance), Factor IV (retardation/depression) and Factor V (sleep disturbance). The results summarized below for each study show that few differences on Factor IV were observed while significant treatment effects were consistently seen on Factor V.

Results for 4 Factors of the HAM-D

	Factor I	Factor III	Factor IV	Factor V
003-002	+	+		+ *
003-003				*
003-020	+ *	+		+ *
003-021				*
003-022	+	+		+ *
003-023		+		+ *
003-024	+ *	+	+	+ *

+ = significant treatment effect at endpoint (Week 6 LOCF)

* = Factor which revealed the most significant differences over the 6 weeks of the trial.

Dropouts

The dropout rates were high (more than 40%) in all but 2 (003-022 and 003-023) of the 003 studies. Most of the dropouts occurred during Week 5; all studies had more than 70% of the patients still on study at Week 4. In 5 of the 7 studies, the primary reason for dropout in the remeron group was lack of efficacy. The percentage of patients dropping due to lack of efficacy in the remeron and placebo groups is shown below for each study. Note that in 3 studies, the percentage of LOE remeron dropouts is greater or equal to the placebo LOE dropouts.

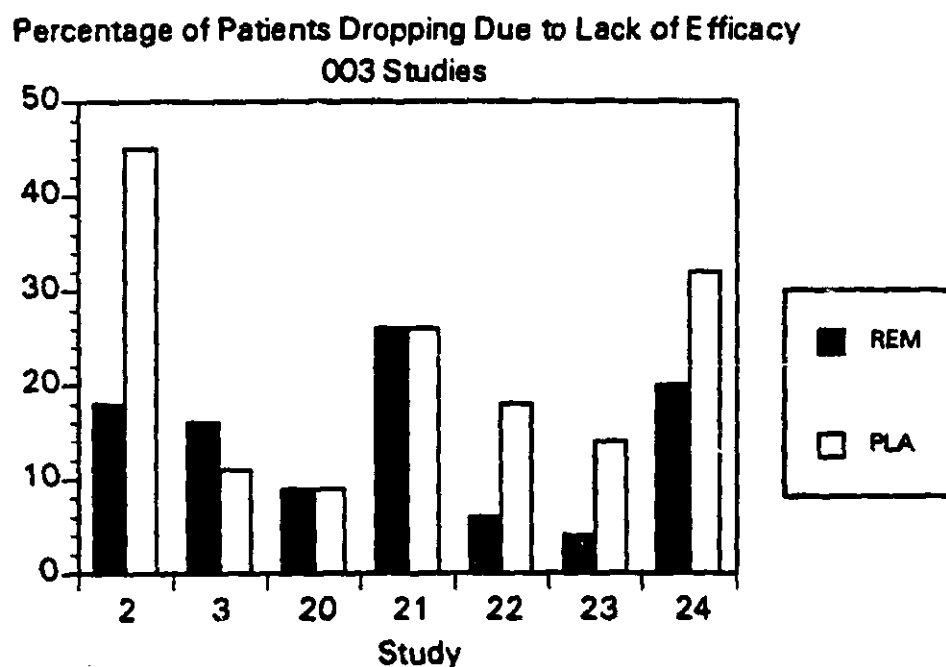


Figure 32

From the table below, it can be seen that the magnitude of the remeron response is larger than the placebo response for each group of patients; dropouts and completers.

It is interesting to note that only 38% of the remeron LOE dropouts were titrated to the maximum dose of 35 mg which is comparable to the percentage of remeron completers titrated to the peak dose.

Table 33. HAM-D 21 Total by Patient Disposition
All 003 Studies Combined

	Remeron Mean (SD)	Placebo Mean (SD)	Amitriptyline Mean (SD)
Lack of Efficacy Dropout			
N (%) ¹	47 (15%)	80 (25%)	15 (8%)
Baseline HAM-D 21	24.9 (3.9)	26.3 (5.2)	28.8 (3.7)
Week 6 LOCF	-2.7 (4.4)	-1.7 (5.6)	-4.6 (4.6)
N (%) ² at Max Dose Allowed	18 (38%)	NA	1 (7%)
Adverse Event Dropout			
N (%)	43 (13%)	38 (12%)	31 (17%)
Baseline HAM-D 21	26.4 (4.4)	25.8 (5.1)	27.4 (6.5)
Week 6 LOCF	-6.9 (7.5)	-3.6 (6.0)	-5.6 (7.7)
N (%) at Max Dose Allowed	1 (2%)	NA	3 (10%)
Other Reason Dropout			
N (%)	15 (5%)	16 (5%)	7 (4%)
Baseline HAM-D 21	25.7 (4.9)	27.8 (5.6)	25.9 (3.2)
Week 6 LOCF	-13.1 (6.1)	-8.3 (6.5)	-14.3 (5.1)
N (%) at Max Dose Allowed	2 (13%)	NA	0 (0%)
Completer			
N (%)	218 (68%)	189 (59%)	134 (72%)
Baseline HAM-D 21	27.2 (5.4)	26.8 (5.1)	28.7 (5.6)
Week 6 LOCF	-14.7 (8.0)	-10.6 (8.6)	-16.1 (7.4)
N (%) at Max Dose Allowed	87 (40%)	NA	25 (19%)

¹ Percentage of patients in the treatment group dropped for this reason.

² Percentage of patients dropping for this reason who took the maximum dose.

Descriptive Statistics by Subgroup

The results by gender and age (<65 vs ≥65) show consistent responses within each treatment group and suggest no statistical interaction between these subgroups and outcome (Table 34).

The results by severity of illness score at baseline show that response is correlated with baseline even within the placebo group (note the sample sizes in the mildly ill group are small thereby producing unreliable estimates) .

**Table 34. HAM-D 21 Total by Subgroup
All 003 Studies Combined**

	Remeron	Placebo	Amitriptyline
Females			
N (%)	166 (51%)	198 (61%)	106 (57%)
Baseline HAM-D 21	27.2 (5.1)	26.8 (5.5)	29.4 (5.7)
Week 6 LOCF	-12.5 (8.6)	-7.1 (8.4)	-13.4 (8.5)
Males			
N (%)	157 (49%)	125 (39%)	81 (43%)
Baseline HAM-D 21	26.2 (5.0)	26.2 (4.5)	27.1 (5.1)
Week 6 LOCF	-11.2 (8.8)	-8.1 (8.8)	-13.4 (8.6)
< 65 Years			
N (%)	295 (91%)	300 (93%)	178 (95%)
Baseline HAM-D 21	26.8 (5.2)	26.8 (5.2)	28.5 (5.5)
Week 6 LOCF	-11.9 (8.9)	-7.5 (8.7)	-13.6 (8.6)
≥ 65 Years			
N (%)	28 (9%)	23 (7%)	9 (5%)
Baseline HAM-D 21	25.7 (4.3)	24.3 (3.3)	28.1 (6.8)
Week 6 LOCF	-11.0 (6.8)	-6.9 (7.2)	-9.8 (7.9)
Mildly Ill at Baseline			
N (%)	16 (5%)	10 (3%)	1
Baseline HAM-D 21	21.9 (2.0)	22.0 (4.3)	20
Week 6 LOCF	-8.9 (5.8)	-8.1 (10.2)	-16
Moderately Ill at Baseline			
N (%)	195 (60%)	209 (65%)	85 (46%)
Baseline HAM-D 21	24.8 (3.6)	24.7 (3.6)	24.7 (3.5)
Week 6 LOCF	-11.1 (7.8)	-7.1 (8.2)	-12.0 (7.5)
Markedly Ill at Baseline			
N (%)	112 (35%)	104 (32%)	101 (54%)
Baseline HAM-D 21	30.8 (5.0)	31.0 (5.0)	31.7 (4.9)
Week 6 LOCF	-13.6 (10.2)	-8.2 (9.2)	-14.5 (9.2)

Overall Conclusions

The table below summarizes this reviewer's interpretations of the results for each study. For study designs, see Tables 2 and 3.

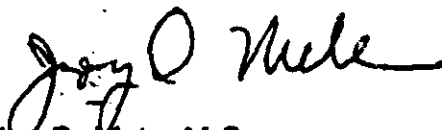
Table 35. Overall Summary

Study	Comments	Statistical Evidence	Page # in Review
003-002	64% of remeron pts. and 44% of placebo pts. completed. Week 5 OC and Week 6 OC results were not significant due to large number of placebo LOE dropouts. LOCF results were positive at every week.	POSITIVE	5-9
003-003	78% of pts. completed 4 weeks and only about 60% completed 6 weeks in each group. More LOE dropouts in remeron group (16%) than the placebo group (11%). No significant treatment differences were observed at any timepoint for any efficacy variable.	NEGATIVE	10-12
003-008	This fixed dose study showed no significant differences between placebo and any of the 4 doses (5, 15, 30 and 60 mg). Dropout rates were high; 40% in placebo group and ≥50% in remeron groups.	NEGATIVE	36-40
003-020	Baseline values indicated that the placebo group was more severely ill at baseline than the remeron group. Baseline-adjusted analyses yielded statistically significant treatment differences at Week 6 (LOCF and OC) for all efficacy variables.	POSITIVE	13-16
003-021	Only 52% of the remeron pts. and 46% of the placebo pts. completed the trial; about 80% completed 4 weeks. Neither the Week 6 OC or Week 6 LOCF results were positive for remeron over placebo. The placebo and amitriptyline completers beat the remeron completers numerically on all variables. Amitriptyline LOCF results were positive.	NEGATIVE	17-24
003-022	The retention rate was high; about 80% of the patients completed the study. Baselines indicate a more severely ill population than what was observed in several other studies. Statistically significant treatment differences were observed on all variables at Week 6 (OC and LOCF) and as early as Week 1 for most variables.	POSITIVE	25-27
003-023	Patients were over 55 years (less than 1/3 of the pts. were 65 or older). HAM-D 21 Total and MADRS results were positive at Week 6, however, results for all other secondary variables were negative. The active control, trazodone, appeared to be under-dosed and showed no significant differences from placebo.	NEGATIVE	28-31
003-024	Almost 90% of the pts. completed 4 weeks; 64% of the remeron pts and 54% of the placebo pts. completed the study. 20% of the remeron pts. and 32% of the placebo pts. dropped due to LOE. Results for all variables were generally in favor of remeron over placebo.	POSITIVE	32-35
84023	This study of hospitalized patients revealed no statistically significant differences between remeron and placebo on any efficacy variable. 20% of the remeron pts and 28% of the placebo pts dropped due to LOE. The max dose allowed in this study was 50 mg. There were 2 suicides in the remeron group.	NEGATIVE	41-44
85027	In this 5-week study, about 78% of the pts. completed. The max dose allowed in this study was 60 mg. The HAM-D 21 Total and GAS results were nearly significant at Week 5 whereas the HAM-D # 1 and the MADRS treatment effects were statistically significant.	SUPPORTIVE	45-47

Evidence for the efficacy of remeron over placebo for the treatment of depression was demonstrated in 4 of the 10 studies reviewed here. One study provided supportive evidence while the remaining 5 studies were negative according to this reviewer's assessment.

The results of the fixed dose study provided no information regarding the optimum dose for efficacy. The mean overall dose in the dose titration studies was 18 mg/day. In 5 of the 7 studies, about ¼ of the patients were titrated to the maximum dose of 35 mg/day. Higher doses in the 2 foreign studies did not result in increased efficacy.

Issues of concern are the large number of dropouts due to lack of efficacy in the remeron groups, the overall large number of dropouts in each study, the absence of significant treatment effects in the one inpatient study and the suggestion from the sponsor's analyses of factors of the HAM-D that the effect on the HAM-D is primarily due to a change in sleep disturbance not retardation and depression.


Joy D. Mele, M.S.
Mathematical Statistician

Concur: Dr. Nevius *SN 10-17-95*

Dr. Dubey *62 10-17-95*

cc:

Orig. NDA 20-416

HFD-120

HFD-120/Drs. Leber, Laughren, Mosholder and Balian

HFD-120/ Mr. David

HFD-713/Dr. Dubey [File: DRU 1.3.2]

HFD-713/Group 2 File

HFD-713/Ms. Mele

HFD-344/Dr. Lisook

Mele/827-1517/SERB/WordPerfect Windows-Remeron.rev/September 7, 1995

This review consists of 60 pages.

OCT 6 1995

NDA: 20-415

Submission Dates:

January 26, 1995

March 20, 1995

April 4, 1995

April 5, 1995

April 12, 1995

April 19, 1995

April 25, 1995

May 2, 1995

May 8, 1995

July 25, 1995

September 1, 1995

COMPLETED

OCT 11 1995

Generic Name, Strength(s), and Formulation: Mirtazapine (Org 3770) 15 and 30 mg
Scored, Film-coated, Oval-Shaped, Immediate Release Tablets for Oral
Administration.

Brand Name: REMERON™

Sponsor: Organon Inc
West Orange, New Jersey

Reviewer: Safaa Ibrahim, Ph.D.

Type of Submission: Review of Original NDA

REVIEW OF ORIGINAL NDA

SYNOPSIS:

REMERON™ (mirtazapine, Org 3770) is a weakly basic tetracyclic compound belonging to the piperazinoazepine group of compounds claiming to possess antidepressant activity. The sponsor is proposing REMERON™ (mirtazapine, Org 3770) as 15 mg and 30 mg scored, film-coated, immediate release tablets for oral administration.

Org 3770 tablets should be administered in the evening preferably prior to sleep. The recommended initial dose is 15 mg daily at bedtime; doses of 15-45 mg/day will be the maintenance dose.

Links have been made between the 15 mg and 30 mg "to-be-marketed" (TBM) tablets and their clinical counterparts. This was based on very rapid and comparable *in vitro* dissolution profiles for the clinical and TBM formulations, and on the fact that both tablet strengths (15 mg and 30 mg) were made from a common granulation. The TBM tablets will be manufactured in Oss, The Netherlands, and no site change is involved.

Org 3770 is rapidly and completely absorbed with a mean peak plasma concentration of 40 ng/mL (CV = 30 %) and a mean T_{max} of 2.2 hours (CV = 68 %) following 15 mg daily doses at bedtime. The mean absolute bioavailability of the tablet is 50 % (CV = 15 %).

Food had no effect on $AUC_{0-\infty}$ or C_{max} of Org 3770 from 15 mg tablets but it increased mean T_{max} by about 50 % (from 1.6 to 2.4 hours). However, the increase in T_{max} is not important as cross study comparisons for T_{max} indicate comparability.

Org 3770 is widely distributed throughout the body with a mean volume of distribution of 4.5 L/kg (CV = 19 %). The drug is 85 % bound to plasma proteins at a concentration range of 0.01-10 μ g/mL, which covers the therapeutic range of the drug. The binding of ORG 3770 to human liver proteins is 2.8 times higher than to human plasma proteins over the same drug concentration range.

Org 3770 is extensively metabolized in man. Less than 1 % of the administered radioactive dose (20 mg (10 μ Ci) of 14 C-ORG 3770) was excreted unchanged in urine. Org 3770 undergoes 8-hydroxylation followed by glucuronide conjugation, N-demethylation followed by sulfate conjugation, N(2)-oxidation, and N-glucuronidation; (see Metabolic scheme in Figure 2).

Org 3770 and the glucuronide of 8-OH metabolite were the major entities circulating in human plasma. Only the N-demethyl Org 3770 was found to be pharmacologically active but it was found at very low levels in human plasma. The predominant metabolite identified in urine was the glucuronide of 8-OH. The focus of the NDA is the parent drug.

An average of 89 % (CV=5 %, n=5) of total radioactive dose was excreted in urine and feces over the 96 hours period. Mean radioactivity was 75 % (CV=13 %, n=5) in urine and 14 % (CV=35 %, n=5) in feces over this period.

An *in vitro* study indicates that four isoenzymes (CYP1A2, CYP2D6, CYP3A4, and CYP2C9) were involved in the formation of Org 3770 metabolites. The prominent metabolite is gluc 8-OH which comes from 8-OH Org 3770. CYP2D6 showed the highest enzymatic activity towards the formation of this metabolite (8-OH), followed by CYP1A2. Polymorphic metabolism may not be expected for Org 3770 since for subjects who are deficient in CYP2D6 (poor metabolizers), the hydroxylation of the drug to 8-OH could be compensated for by CYP1A2.

Cigarette smoking (which is known to induce CYP1A2) increased the mean oral clearance of Org 3770 by about 30 % [50 L/hr (CV = 30 %) nonsmokers (n=35 males) versus 66 L/hr

(CV = 42 %) smokers (n=13 males), see Figure 3].

The other isozymes (CYP3A4 and CYP2C9) were involved in the formation of minor metabolites (viz., N-demethyl metabolite and N-oxide).

The degree of accumulation is minimal (about 1.5) and is independent of the dose. Steady-state levels of Org 3770 were reached within 5 days.

The drug displays linear kinetics over the dosage range of 15-80 mg when it was administered daily in the morning and also over the dosage range of 15-75 mg when it was administered daily in the evening.

Mean oral clearance of Org 3770 in healthy nonsmoking young volunteers was 0.7 L/hr/kg (CV = 30 %, n = 35 males). Mean elimination half-life was 22 hours (SD = 5 hours, n = 27 males).

Oral clearance (CL/F) of Org 3770 was 40 % lower in elderly males (n=8, mean age = 69 years) than young males (n=9, mean age = 32 years) (0.40 L/hr/kg versus 0.70 L/hr/kg, respectively). Clearance was comparable between elderly females and elderly males.

Young females (n=9, mean age = 38 years) had a 45 % lower oral clearance than young males (n=9, mean age = 32 years) (0.38 L/hr/kg versus 0.70 L/hr/kg, respectively).

The effect of race on Org 3770 pharmacokinetics has not been studied.

Patients with moderate (n=8, GFR=11-39 mL/min/1.73 m²) and severe (n= 10, GFR ≤ 10 mL/min/1.73 m²) renal function had mean oral clearance (CL/F) 30 % and 50 % lower than normal subjects; 0.40 moderate; 0.30 severe, and 0.60 normals; units L/hr/kg. One-half of the normal adult starting dose should be recommended for these renally impaired patients. This would be feasible since both strengths of Org 3770 tablets (15 mg and 30 mg) are scored.

Oral clearance of Org 3770 was reduced by 30 % in mild to moderate hepatically impaired patients (n=8, mean age = 67 years) compared to normal subjects (n=8, mean age = 68 years); 0.33 L/hr/kg hepatic vs 0.50 L/hr/kg normal. One-half of the normal adult starting dose should be recommended in hepatically impaired patients. Decreased clearance could be quite pronounced in severely hepatically impaired patients.

The effect of alcohol and diazepam on plasma levels of Org 3770 is minimal.

A pilot study suggests that a dosage range of 10-35 mg/day of Org 3770 may be effective in the treatment of major depression.

The sponsor provided *in vitro* dissolution profiles for the clinical tablet (Biobatch

No. CP 87064, 15 mg tablets) and the final "to-be-marketed" (TBM) tablets (15 mg and 30 mg tablets). Based on the results provided, the following dissolution methodology and specification is recommended for both strengths of Org 3770 tablets (15 mg and 30 mg):

Apparatus:
Paddle speed:
Medium:
Specification:

RECOMMENDATION:

The NDA # 20-415 that was filed for REMERON™ (mirtazapine, Org 3770) 15 mg and 30 mg tablets on January 26, 1995 has been reviewed and has been found to be acceptable for meeting the Division of Biopharmaceutics' requirements. Comment 1 is for the Chemist; Comments # 2 and 3 are for the Medical Officer. The sponsor is requested to pursue Comments # 4 and 5 and adopt dissolution methodology and specification as outlined in Comment # 6.

Pharmacokinetic labeling is included in this review package.

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APPENDIX I - (Individual Study Reports)

In Vivo Studies:

ADME

- Biotransformation of Org 3770 in Man and Laboratory Animals** 22
(Protocol 85138).
- ADME Study in 6 Healthy Male Volunteers Using a Single Oral Dose of** 26
15 mg Org 3770 Consisting of 50% ¹³C-Labelled Org 4419 (-) and 50%
Unlabelled Org 4420 (+) (the Enantiomers of ORG 3770) (Protocol 22501).

ABSOLUTE BIOAVAILABILITY:

- Absolute Bioavailability of Org 3770 Tablets in Healthy Male Subjects After Single and Multiple Oral Dosing (Protocol 88024). __30

DOSE PROPORTIONALITY:

- Pharmacokinetics of Org 3770 in Young Healthy Male Volunteers After a Single Oral Administration of 30 or 45 mg: Dose Linearity Testing (Protocol 86020). __34
- Pharmacokinetics of Org 3770 in Young Healthy Male Volunteers After Sub-Chronic Oral Administration of Escalating Daily Doses (15-80 mg): Dose Linearity Testing (Protocol 87003). __36
- Pharmacokinetics of Org 3770 in Young Healthy Male Subjects Receiving Escalating Daily Doses (15, 30, 45, 60, and 75 mg) (Protocol 003-011). __40

FOOD EFFECT:

- The Effect of a High Fat Meal on the Oral Bioavailability of a 15 mg Org 3770 Tablet in Nineteen Normal, Healthy Subjects (Protocol 003-012). __44

BIOEQUIVALENCE:

- Assessment of Bioequivalence of Four Oral Org 3770 Formulations (30 mg tablet, 15 mg tablet, 5 mg tablet and 5 mg capsule) in Healthy Young Male Subjects (Protocol 88003). __47

SPECIAL POPULATIONS:

- Age and Gender: A Pharmacokinetic Study of Org 3770 in Healthy Normal Adult and Elderly Volunteers (Protocol 003-006). __52

Race: (Has not been studied)

- Renal Impairment: A Clinical Study to Assess the Effect of Renal Impairment on the Pharmacokinetics of Org 3770 (Protocol 22503). __57

- Hepatic Impairment: An Open, Single-Dose Pharmacokinetic Study with 15 mg Org 3770 Administered Orally in a Group of Elderly Subjects with Hepatic Disease and an Age-Matched Control Group (Protocol 88007). __61

DRUG-DRUG INTERACTIONS:

- Clinical Interaction Study Org 3770/Alcohol: Org 3770 Plasma Levels and __65

Pharmacokinetic Evaluation (Protocol 85147).

- Actions and Interactions of Psychotropic Drugs on Human Performance and Mood: Single Doses of Org 3770, Amitriptyline, and Diazepam (Mattila M., et. al., Pharmacology and Toxicology 1989, 65: 81 - 88). _67

PHARMACODYNAMIC ANALYSIS:

- Org 3770 Dose-Finding Study in Moderately Depressed Patients (Protocol 003-001). _75

In Vitro Studies:

PLASMA AND LIVER PROTEINS:

- Binding of Org 3770 to Human Plasma Proteins and Human Liver Proteins (Protocol 2157). _80

ISOENZYME DETERMINATION:

- Characterization of Human Cytochrome P450 Isoenzymes Involved in the *In Vitro* Metabolism of Org 3770 (Protocol SDGRR 4077). _82

APPENDIX II - (Drug Formulation)

APPENDIX III - (Dissolution)

APPENDIX IV - (Analytical Methodology)

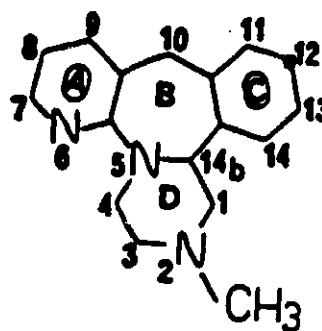
APPENDIX V - (Firm's Proposed Labeling)

(Note: The appendices (I-V) contain more detailed data/information such as individual study reports, dissolution methodology and specification, assay methodology and validation, formulation of dosage forms, and the firm's proposed labeling. This information is being retained in the Division of Biopharmaceutics, and can be obtained upon request)

BACKGROUND

REMERON™ (mirtazapine, Org 3770) is a weakly basic tetracyclic antidepressant belonging to the piperazinoazepine group of compounds. The sponsor mentions that Org 3770 is an alpha2-antagonist with antiserotonin activity.

Org 3770 is: ($\pm$)-1,2,3,4,10,14b-hexahydro-2-methylpyrazino [2,1-a] pyrido [2,3-c] benzazepine. It has the empirical formula of $C_{17}H_{19}N_3$ and molecular weight of 265. The structural formula is shown in Figure 1.



Org 3770

C-14b = Chiral Center

PHYSICOCHEMICAL PROPERTIES:

Mirtazapine (Org 3770) is a white to creamy crystalline powder. It is practically insoluble in water, freely soluble in n-hexane and diethyl ether, and moderately soluble in toluene and methanol. The pKa of the drug in 66 % v/v aqueous methanol solution is 7.4. The partition coefficient has not been determined.

Org 3770 is a racemic mixture consisting of two enantiomers, (-)-enantiomer (Org 4419) and (+)-enantiomer (Org 4420). The focus of this NDA is the racemate.

INDICATION AND USAGE:

REMERON (mirtazapine, Org 3770) is indicated for the treatment of major depression.

HOW SUPPLIED:

REMERONTM (mirtazapine, Org 3770) is supplied for oral administration as 15 mg and 30 mg scored, film-coated, oval-shaped immediate release tablets. The 15 mg tablet is yellow with "Organon" embossed on one side and "TZ3" on the other side. The 30 mg tablet is red-brown with "Organon" embossed on one side and "TZ5" on the other side.

DOSAGE AND ADMINISTRATION (FIRM'S):

REMERON (mirtazapine, Org 3770) tablets should be administered in the evening preferably at bedtime. The recommended initial dose is 15 mg daily at bedtime. Patients dosed in a range of 15-45 mg/day in clinical studies demonstrated antidepressant effectiveness of REMERON. Patients not responding to the initial 15 mg/day dose may benefit from dose increases of up to a maximum of 45 mg/day.

MANUFACTURER AND MANUFACTURING SITE:

Mirtazapine 15 mg and 30 mg tablets will be manufactured by N.V. Organon, Oss, The Netherlands. Tablets will be packaged, tested and released by Organon Inc., New Jersey, U.S.A.

FOREIGN MARKETING:

Org 3770 has received approval in the Netherlands and Austria. Approval is pending in some other countries (e.g. Australia, Finland, Norway).

SUMMARY OF HUMAN BIOAVAILABILITY/PHARMACOKINETICS AND PHARMACODYNAMICS

I. BIOAVAILABILITY:

The mean absolute bioavailability of Org 3770 tablets was about 50 % (CV = 15 %) following 15 mg daily morning doses for 7 days to 8 healthy male volunteers (Protocol 88024).

II. PHARMACOKINETICS:

Plasma levels of Org 3770 appear to follow a 2-compartment model with 1-first order absorption and elimination.

A. Absorption:

Org 3770 is rapidly and completely absorbed. Following multiple oral doses of 15 mg/day at bedtime for 5 days to 27 healthy male volunteers, mean peak plasma concentration was 40 ng/mL (CV = 30 %) with a T_{max} of 2.2 hours (CV = 68 %) (Protocol 003-011).

B. Distribution:

Mean volume of distribution determined after a single IV infusion over 1 hour of 3.5 mg [¹³C]-Org 3770 to 8 healthy male volunteers (Protocol 88024) is 4.5 L/kg (CV = 19 %). This value exceeds the volume of the total body water (0.9 L/kg), indicating that Org 3770 is widely distributed throughout the body.

C. Metabolism:

(i) Metabolic Profile:

Org 3770 is extensively metabolized in man (Protocol 85138). Less than 1 % of administered radioactive dose (20 mg (10 μ Ci) of 14 C-labelled Org 3770) was excreted unchanged in urine. Five metabolic pathways were identified for Org 3770 (See Figure 2). These included:

- A. C(8) Hydroxylation (8-OH-) followed by glucuronide conjugation
- B. C(13) Hydroxylation (13-OH-) followed by glucuronide conjugation
- C. N(2) Demethylation (des-) followed by sulfate conjugation
- D. N(2) Oxidation
- E. N(2) glucuronidation

Org 3770 and the glucuronide of 8-OH metabolite were the major entities circulating in human plasma. Only the N-demethyl Org 3770 was found to be pharmacologically active but it was found at very low levels in human plasma. The most predominant metabolite identified in urine was the glucuronide of 8-OH.

(ii) Mass Balance:

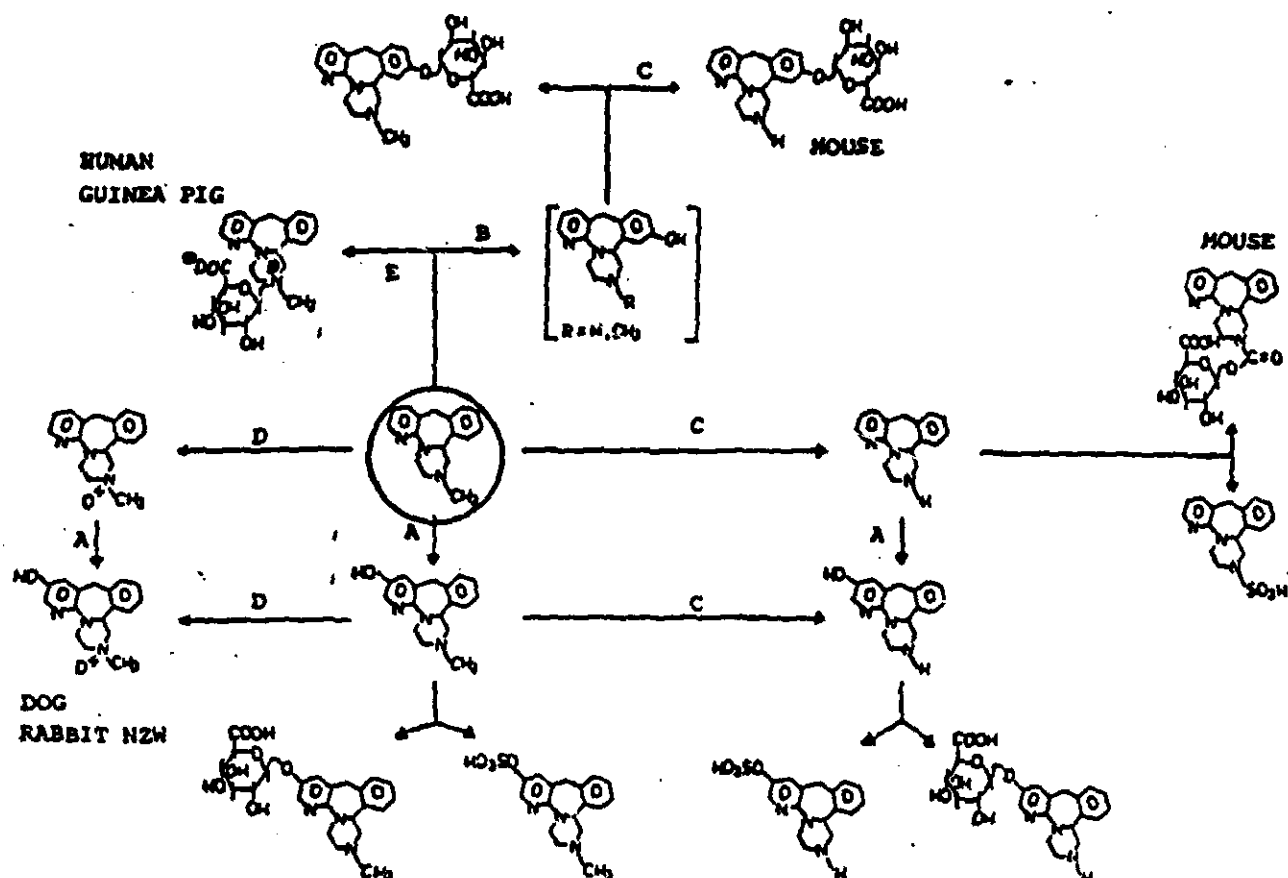
An average of 89 % (CV=5 %, n=5) of total administered radioactive dose was excreted in urine and feces over 96 hours. Mean radioactivity was 75 % (CV=13 %, n=5) in urine and 14 % (CV=35 %, n=5) in feces over this period.

(iii) Cytochrome P-450 Isozymes Which are Responsible for Org 3770 Metabolism:

In an *in vitro* enzymatic study (Protocol SDGRR 4077), four isoenzymes (CYP1A2, CYP2D6, CYP3A4, and CYP2C9) were involved in the formation of Org 3770 metabolites. The prominent metabolite is gluc 8-OH which comes from 8-OH Org 3770. CYP2D6 showed the highest enzymatic activity towards the formation of this metabolite, viz., 8-OH, followed by CYP1A2. Polymorphic metabolism may not be expected since subjects who are deficient in CYP2D6 (poor metabolizers), the hydroxylation of the drug to 8-OH could also occur by CYP1A2.

Cigarette smoking (which induces CYP1A2) increased the mean oral clearance of Org 3770 by about 30 % [50 L/hr (CV = 30 %) nonsmokers (n=35 males) versus 66 L/hr (CV = 42 %) smokers (n=13 males); $p < 0.05$; see Figure 3] (Data were pooled from studies # 88024, 86620, 003-012, and 22503).

Figure 2: Biotransformation scheme of Org 3770



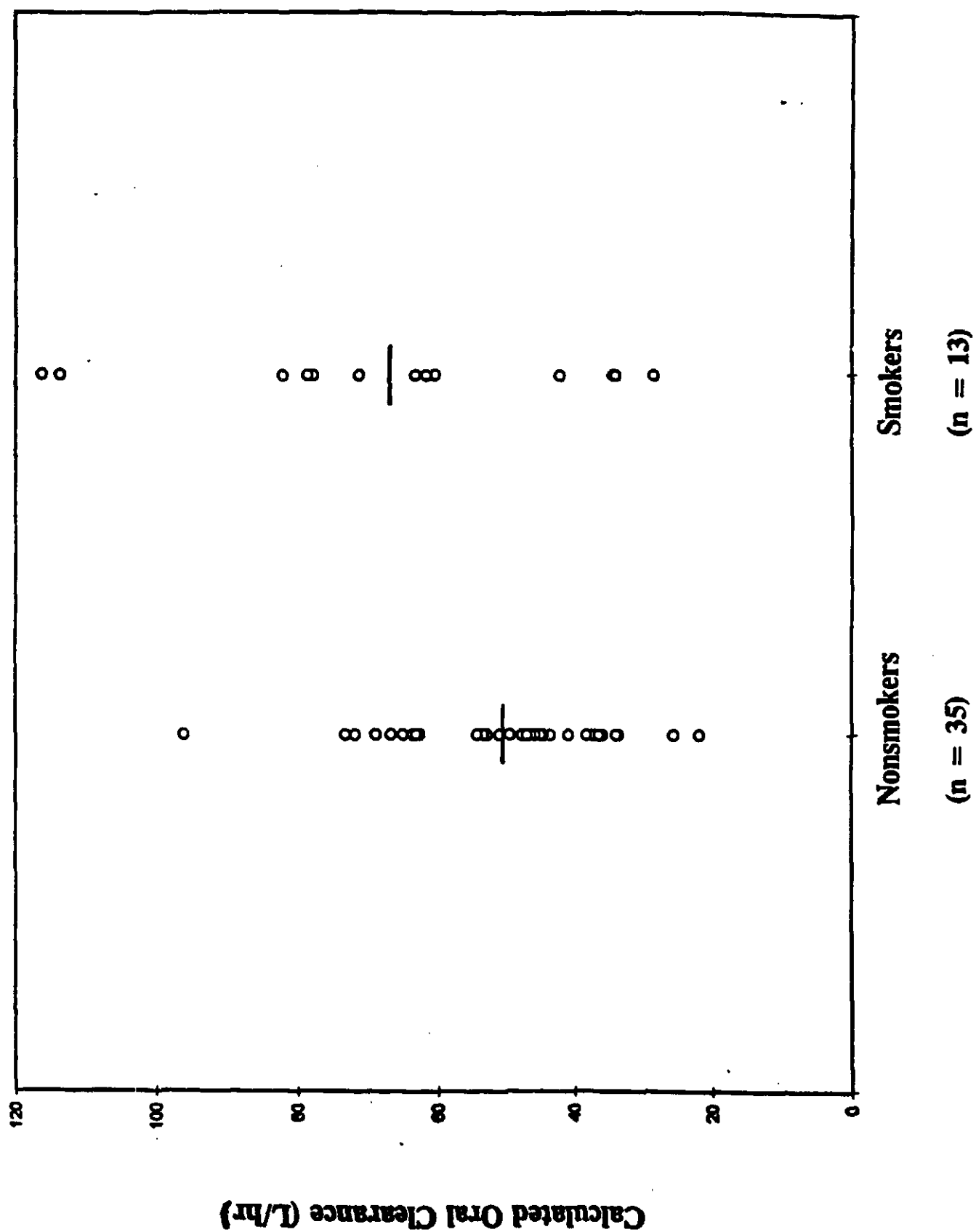
Species-specific routes are indicated

Biotransformation is limited to the following pathways;

- A 8-hydroxylation followed by conjugation
- B 13-hydroxylation followed by conjugation
- C N(2) demethylation followed by conjugation
- D N(2) oxidation
- E N(2) glucuronidation

Structure in brackets has not been found, but is expected to be an intermediate.

Figure 3



The other isozymes (CYP3A4 and CYP2C9) were involved in the formation of the minor metabolites (viz., N-demethyl metabolite and N-oxide).

D. Elimination:

Mean oral clearance of Org 3770 in healthy nonsmoking volunteers was 0.7 L/hr/kg (CV = 30 %, n=35 males). Mean elimination half-life was 22 hours (CV = 23 %, n= 27 males).

Although the focus of this NDA is the racemate, the sponsor has characterized the pharmacokinetics of the enantiomers of Org 3770 in a single-dose study involving 6 healthy male volunteers (Protocol 22501). Each volunteer received a single oral dose of 15 mg of the pseudoracemate of Org 3770, i.e. a mixture of 50 % ¹³C-labelled Org 4419 (-) and 50 % unlabelled Org 4420 (+). It was found that the (-) enantiomer (Org 4419) had higher C_{max} (1.5-fold), longer elimination $t_{1/2}$ (2-fold) and greater $AUC_{0-\infty}$ (3-fold) than the (+) enantiomer (Org 4420).

Interconversion of the enantiomers is not likely, since different biotransformation pathways are involved in their metabolism. The (-) enantiomer is cleared preferably via N-glucuronidation, whereas the (+) enantiomer is cleared preferably via 8-hydroxylation followed by glucuronidation.

III. DOSE PROPORTIONALITY:

Dose proportionality of Org 3770 was assessed in several studies.

In a double-blind, parallel, single-dose study (Protocol 86020) involving 16 healthy male subjects, dose-proportionality of Org 3770 was assessed at two dose levels: 30 mg (n=6 on drug and n=2 on placebo) and 45 mg (n=6 on drug and n=2 on placebo). No significant differences were found in dose-normalized (to 1 mg) $AUC_{0-\infty}$ and C_{max} values between the single 30 and 45 mg oral doses of Org 3770, indicating dose-linearity within this range.

In a double-blind, dose rising, multiple-dose study (Protocol 87003), the dose-proportionality of Org 3770 was assessed in 8 healthy male volunteers (n=6 on drug and n=2 on placebo) given daily morning doses of 15 mg/day (for 4 days), 30 mg/day (for 4 days), 45 mg/day (for 3 days), 60 mg/day (for 3 days), and 80 mg/day (for 3 days).

No significant differences were noted in dose-normalized (to 1 mg) AUC_{0-24hr} , C_{max} , and $C_{min(0)}$ values among the doses administered, indicating that Org 3770 exhibits linear kinetics over the range of 15 mg to 80 mg oral morning doses administered once daily for 3-4 days; this covers the therapeutic range for the drug.

The dose proportionality of Org 3770 was also assessed in another multiple-dose, open-label,

dose-rising study (Protocol 003-011) involving 27 healthy male subjects; a larger study than the previous one. Each subject received daily oral doses in the evening at 10 p.m. of 15, 30, 45, 60, and 75 mg/day for 5 days.

This study also demonstrated that Org 3770 displays linear kinetics following daily evening doses of 15 to 75 mg/day for 5 days; this covers the therapeutic range for the drug.

Steady-state was attained within 5 days.

IV. FOOD EFFECT:

The effect of food on the oral bioavailability of a 15 mg Org 3770 tablet was studied in 19 healthy male volunteers in a single dose, 2-way crossover study (Protocol 003-012). Each subject received a single 15 mg dose after an overnight fast or along with a standard high fat breakfast (2 slices of toasted white bread spread with butter, 2 eggs fried in butter, 2 slices of bacon, 2 oz. of hash-browned potatoes, and 8 oz. of whole milk).

Food increased mean T_{max} of Org 3770 by 50% (from 1.6 to 2.4 hours), but had no effect on mean $AUC_{0-\infty}$ or C_{max} .

V. BIOEQUIVALENCE:

The initial to be marketed (TBM) 1 X 30 mg tablet (Batch No.: CP 87089) (Test), clinical 6 X 5 mg tablets (Batch No.: CP 83095) (Test), and clinical 6 X 5 mg capsules (Batch No.: CP 86098) (Test) were compared to the clinical/initial TBM 2 X 15 mg tablets (Batch No.: CP 87064) (Reference) in a single-dose study (Protocol 88003) involving 22 healthy male volunteers.

The focus of the NDA program is the 15 mg and 30 mg tablets. It is seen that the 1 X 30 mg tablet was found to be equivalent to the 2 X 15 mg tablet (reference) with respect to $AUC_{0-\infty}$ (93-110 %). However, it was inequivalent in terms of C_{max} (77-106 %). C_{max} was slightly lower in this single dose study. The drug will be dosed chronically and in the treatment of this disease, the extent of exposure is more important than C_{max} . Therefore, the slight falling of C_{max} outside the interval in a single dose study is unimportant clinically.

The initial TBM ~~prospective~~ 15 mg (Batch No. CP 87064) and 30 mg (Batch No.: CP 87089) tablets differed slightly from the final TBM tablets with respect to the amounts of magnesium stearate and coating ingredients (See APPENDIX II). The final TBM (15 mg and 30 mg tablets) formulations have not been used in any of the clinical and/or pharmacokinetic studies.

this was the case for the initial TBM formulations as well as will be the case for the final TBM formulations. Thus, a request for a waiver from participation of TBM tablets in a biostudy was submitted. Link between the TBM and the clinical/prospective tablets is based on the comparison of their dissolution profiles

at 50 rpm, See APPENDIX III)]

VI. SPECIAL POPULATIONS:

A. Effect of Age:

Oral clearance (CL/F) of Org 3770 was 40 % lower in elderly males (n=8, mean age = 69 years) than in young males (n=9, mean age = 32 years) (0.40 L/hr/kg versus 0.70 L/hr/kg, respectively) following daily 20 mg oral doses at bedtime for 7 days (Protocol 003-006).

CL/F was reduced by only 10 % in elderly females (n=8, mean age = 68 years) compared to young females (n=9, mean age = 38 years) (0.34 L/hr/kg versus 0.38 L/hr/kg, respectively). Clearance was comparable between elderly females and elderly males.

Dosing adjustment may not be necessary in elderly but they may need to be closely monitored for adverse effects.

B. Effect of Gender:

Following daily 20 mg oral doses of Org 3770 at bedtime for 7 days (Protocol 003-006), young females (n=9, mean age = 38 years) had a 45 % lower oral clearance than young males (n=9, mean age = 32 years) (0.38 L/hr/kg versus 0.70 L/hr/kg, respectively).

Elderly females (n=8, mean age = 68 years) had only a 15 % decrease in oral clearance than elderly males (n=8, mean age = 69 years) (0.34 L/hr/kg versus 0.40 L/hr/kg, respectively).

Variability (% CV) in CL/F was not affected by age or gender, and was about 45 %.

Dosing adjustment may not be necessary in young females but they may need to be closely monitored for adverse effects.

Accumulation of Org 3770 was minimal (about 1.5) and was independent of age and gender.

C. Effect of Race: (Has not been studied)

D. Effect of Renal Disease:

Following a single 15 mg oral dose (Protocol 22503), the kinetics of Org 3770 in patients with mild renal function (GFR=40-79 mL/min/1.73 m², n=10) were similar to those in normal subjects (GFR ≥ 80 mL/min/1.73 m², n=10). However, in patients with moderate

(GFR = 11-39 mL/min/1.73 m², n=8) and severe (GFR ≤ 10 mL/min/1.73 m², n=10) renal function, mean oral clearance (CL/F) of Org 3770 was reduced by about 30 % and 50 %, respectively, compared to normal subjects; 0.40 moderate; 0.30 severe, and 0.60 normals; units L/hr/kg.

Mean elimination half-life ($t_{1/2}$) was similar in mild and moderate renal patients ($t_{1/2}$ = 34 and 36 hours, respectively) compared to normal subjects ($t_{1/2}$ = 33 hours). However, it increased by about 27% in severe renal patients compared to normals ($t_{1/2}$ = 42 hours versus 33 hours, respectively).

Accumulation of Org 3770 is expected in patients with moderate to severe renal function upon daily oral administration. One-half of the normal starting adult dose should be recommended for them. This would be feasible since both Org 3770 tablet strengths (15 mg and 30 mg) are scored.

E. Effect of Hepatic Disease:

Following a single 15 mg oral dose (Protocol 88007), the elimination half-life of Org 3770 was prolonged by 35% (32 vs 44 hours) and its clearance was reduced by 30% (0.50 versus 0.33 L/hr/kg) in mild to moderate hepatically impaired patients (n=8, mean age = 67 years) compared to normal subjects (n=8, mean age = 68 years). Accumulation may occur in hepatically impaired patients upon once daily oral administration of Org 3770; further, these patients should be closely monitored for adverse effects. One-half of the normal adult starting dose should be recommended in hepatically impaired patients.

VII. DRUG INTERACTIONS:

A. Ethanol:

Concomitant administration of ethanol (single 60 g oral dose) had minimal effect on the plasma levels of Org 3770 (15 mg) in 6 healthy male subjects (Protocol 85147).

B. Diazepam:

Coadministration of diazepam (single 15 mg oral dose) with Org 3770 (15 mg) in 12 healthy volunteers (7 males and 5 females) showed that plasma concentrations of either drug were unaffected when compared to each drug administered alone.

VIII. PHARMACODYNAMIC ANALYSIS:

In an open-label, pilot efficacy dose-finding study (Protocol 001-001), the relationship between 17-item HAM-D scores and the oral dose of Org 3770 was investigated in 12

moderately depressed patients (6 males and 6 females). Org 3770 was administered as oral doses daily at bedtime. The treatment period was 28 days. It began with a titration phase (Days 0-4) with dosages (5-10 mg/day) being incremented every three to four days to an effective dose (15-35 mg/day) level. Patients were maintained on the effective dose level (15-35 mg/day) for the remaining period of the study. No blood samples were taken.

The % reduction from baseline in mean 17-Item HAM-D scores was 37 % at Week 0.5, 56 % at Week 1, 70 % at Week 2, 65 % at Week 3, and 70 % at Week 4.

Eight of 12 patients (67 %) achieved at least the ≥ 50 % reduction criterion by Week 1, and 10 (91%) of 11 patients evaluated achieved this criterion by Week 2. Six of the ten patients who achieved the ≥ 50 % reduction criterion by Week 2 were receiving 25-35 mg Org 3770. The other four were at doses of 10-15 mg/day.

This pilot study suggests that a dosage range of 10-35 mg/day of Org 3770 may be effective in the treatment of major depression.

IX. PROTEIN BINDING:

An equilibrium dialysis study (Protocol 2157) has shown that mean (SD) percent bound of Org 3770 to human plasma proteins is 85 % (2.2). Binding is reversible and concentration-independent over the range of 0.01-10 $\mu\text{g/mL}$, this covers the therapeutic range for the drug. In the same study, it was shown that the binding of Org 3770 to human liver proteins is 2.8 times higher than to human plasma proteins and this was also concentration-independent over the range of 0.01-10 $\mu\text{g/mL}$.

X. FORMULATION:

REMERON™ (mirtazapine, Org 3770) is proposed for marketing as 15 mg and 30 mg scored, film-coated, oval-shaped immediate release tablets. Both the 15 mg and 30 mg tablets are made from a

The quantitative composition of Org 3770 eventual to be marketed tablet formulations are as follows:

<u>Tablet Core</u>	<u>15 mg Tablet</u>	<u>30 mg Tablet</u>
Mirtazapine	15 mg	30 mg

* The amount of magnesium stearate can vary $\pm 10\%$ of the stated amount.

Details of the composition of formulations used in the clinical trials (US and Europe) and the final "to be marketed" (TBM) formulations are presented in APPENDIX II; see also Bioequivalence section.

XI. IN VITRO DISSOLUTION:

15 mg Tablets: Clinical Batch No. CP 87064 which participated in several biostudies and clinical studies, and 3 stability (final to be marketed) batches (Batch No.: 02-1127-000, 02-1128-000, and 02-1129-000).

30 mg Tablets: Three stability (final to be marketed) batches (Batch No.: 02-1124-000, 02-1125-000, and 02-1126-000).

Both tablet strengths (15 mg and 30 mg) showed rapid dissolution in 15 minutes) in 0.1 N HCL (physiologically relevant medium). Formulation links (clinical and TBM) were established based on very rapid and comparable dissolution profiles amongst all batches of the two tablet strengths (15 mg and 30 mg).

The Division of Biopharmaceutics recommends the following dissolution method and specification for both strengths of mirtazapine tablet – 15 mg and 30 mg:

Apparatus:

Paddle speed:

Medium:

Specification:

(See APPENDIX II and III for more detailed information on dissolution and formulation links)

XII. ANALYTICAL METHODOLOGY:

(Detailed assay methodology and validation are presented in APPENDIX IV)

COMMENT TO THE CHEMIST:

(1) The Chemist is requested to examine the stability profiles of the two halves of the scored tablet.

COMMENTS TO THE MEDICAL OFFICER:

(2) Significant age and gender effect were noted in the pharmacokinetics of Org 3770. Elderly male subjects had a 40 % lower clearance than young male subjects. Young female subjects had a 45 % lower clearance than young male subjects.

(3) Moderate and severely renally impaired patients had 30 % and 50 % lower clearance than normal subjects. Clearance was also reduced by 30 % in hepatic patients as compared to normals. One-half of the normal adult starting dose should be recommended for both renally and hepatically impaired patients. This would appear feasible since both strengths of Org 3770 tablets (15 mg and 30 mg) are scored.

COMMENTS TO BE SENT TO THE FIRM:

(4) The sponsor is encouraged to perform *in vitro* enzymatic experiments on Org 3770 with others inhibitors or substrates of CYP1A2 (e.g. theophylline and cimetidine) and CYP2D6 (e.g. tricyclic antidepressants and selective serotonin reuptake inhibitors).

(6) The sponsor is requested to adopt the following dissolution methodology and specification for both strengths of mirtazapine tablets (15 mg and 30 mg):

Apparatus:

Paddle speed:

Medium:

Specification:

PHARMACOKINETIC LABELING IS PROVIDED BELOW:

PHARMACOKINETICS:

Absorption, Distribution, Metabolism, and Excretion:

Mirtazapine is rapidly and completely absorbed following oral administration to healthy volunteers. Peak plasma drug concentrations were attained within 2 hours. Mean absolute bioavailability of mirtazapine from tablets is 50 % (CV = 15 %). Food did not affect the rate or extent of drug absorption.

Mirtazapine is widely distributed throughout the body with a mean volume of distribution of 4.5 L/kg (CV = 19 %). The binding of the drug to human plasma proteins is 85 %. Binding to plasma proteins is reversible and independent over the concentration range of 0.01-10 µg/mL. The binding of mirtazapine to human liver proteins is 2.8 times higher than to human plasma proteins and is also concentration-independent.

Mirtazapine is extensively metabolized in man. Less than 1 % of the administered radioactive

dose is excreted unchanged in urine. Mirtazapine and the 8-OH glucuronide metabolite were the major entities circulating in human plasma. The predominant metabolite identified in urine was 8-OH glucuronide.

Mean radioactivity was 75 % (CV=13 %, n=5) in urine and 14 % (CV=35 %, n=5) in feces over a 96-hour period for a combined recovery of 89 %.

Mean oral clearance of mirtazapine in healthy young volunteers was 0.70 L/hr/kg (CV = 30 %, n = 35 males) and the mean elimination half-life was 22 hours (SD = 5 hours, n = 27 males).

Steady-state plasma levels of mirtazapine were attained within 5 days. The degree of accumulation of the drug is minimal (1.5). Mirtazapine exhibits linear kinetics over the range of 15-75 mg doses administered daily at bedtime.

SPECIAL POPULATIONS:

Effect of Age:

Following oral administration of 20 mg/day for 7 days at bedtime, oral clearance of mirtazapine was 40 % lower in elderly males (n=8, mean age = 69 years) than in young males (n=9, mean age = 32 years), (0.40 L/hr/kg versus 0.70 L/hr/kg).

(See Precaution Section)

Effect of Gender:

Following oral administration of 20 mg/day for 7 days at bedtime, young females (n=9, mean age = 38 years) had 45 % lower oral clearance than young males (n=9, mean age = 32 years), (0.38 L/hr/kg versus 0.70 L/hr/kg). Clearance was comparable between elderly females and elderly males. (See Precaution Section)

Effect of Race: No specific study was conducted to investigate the effect of race on the pharmacokinetics of mirtazapine.

Effect of Renal Disease:

Following a single 15 mg oral dose, patients with moderate (GFR=11-39 mL/min/1.73 m², n=8) and severe (GFR ≤ 10 mL/min/1.73 m², n=10) renal function had mean oral clearance of mirtazapine reduced by about 30 % and 50 %, respectively, compared to normal subjects; 0.4 moderate, 0.30 severe, and 0.60 normals; units L/hr/kg.

Dosage adjustment may be necessary in patients with moderate and severe renal impairment. (See PRECAUTIONS and DOSAGE AND ADMINISTRATION)

Effect of Hepatic Disease:

Following a single 15 mg oral dose, oral clearance of mirtazapine was reduced by 30% in hepatic patients (n=8, mean age = 67 years) compared to normal subjects (n=8, mean age = 68 years) – 0.33 L/hr/kg hepatic versus 0.50 L/hr/kg normals.
(See PRECAUTIONS and DOSAGE AND ADMINISTRATION)

Effect of Cigarette Smoking:

Cigarette smoking increased the mean oral clearance of mirtazapine by 30 % [50 L/hr (CV = 30 %) nonsmokers (n=35 males) versus 66 L/hr (CV = 42 %) smokers (n=13 males).

PRECAUTIONS

Drug Interactions:

Cytochrome P-450 Isozymes Which are Responsible for the Metabolism of Mirtazapine:

An *in vitro* enzymatic study indicated that four isoenzymes (CYP1A2, CYP2D6, CYP3A4, and CYP2C9) were involved in the formation of Org 3770 metabolites. In human plasma, the prominent metabolite is 8-OH glucuronide which comes from 8-OH mirtazapine. CYP2D6 showed the highest enzymatic activity towards the formation of the 8-OH metabolite followed by CYP1A2.

Other isozymes (CYP3A4 and CYP2C9) were involved in the formation of the minor metabolites (viz., N-demethyl metabolite and N-oxide).

Alcohol:

Concomitant administration of alcohol (equivalent to 60 g) had minimal effect on plasma levels of mirtazapine (15 mg) in 6 healthy male subjects.

Diazepam:

Concomitant administration of diazepam (15 mg) had minimal effect on plasma levels of mirtazapine (15 mg) in 12 healthy subjects (5 females and 7 males).

Use in elderly, young females, and renally and hepatically impaired patients:

Mirtazapine tablets should be used with caution in elderly, young females, and renally and hepatically impaired patients due to a decrease in the clearance of the drug.

DOSAGE AND ADMINISTRATION

Use in Renally Impaired Patients: One-half of the normal adult starting dose should be administered to moderately (GFR = 11-39 mL/min/1.73 m²) and severely (GFR ≤ 10 mL/min/1.73 m²) renally impaired patients.

Use in Hepatically Impaired Patients: One-half of the normal adult starting dose should be administered to hepatically impaired patients.

Safaa Ibrahim, 10/2/95

Safaa S. Ibrahim, Ph.D.

Pharmacokinetics Evaluation Branch I

Biopharm Day on August 10, 1995.

RD/FT initialed by R. Baweja, Ph.D. *R. Baweja* 10/6/95.

cc: NDA # 20-415 (Orig.), HFD-120, HFD-426 (Ibrahim, Baweja, Fleischer), HFD-427 (ChenMe), Chron, Drug, HFD-19 (FOI), HFD-340 (Viswanathan), F, DI, G, RI, and Reviewer Files.

REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA

IND

Reviewer: Gary Evoniuk, Ph.D.
Date: November 16, 1990

Sponsor: Organon Inc.
West Orange, NJ

Drug: ORG 3770 (6-azamianserin)

Pharmacologic Category: Antidepressant

Studies Reviewed:

A. An 18 month carcinogenicity feeding study in mice with ORG 3770

B. A 24 month feeding study in rats with ORG 3770

Note - Portions of this review were excerpted directly from the sponsor's submission.

Toxicology

A. An 18 month carcinogenicity feeding study in mice with ORG 3770

A total of 400 CD-1 mice were subdivided into the following groups:

<u>Group</u>	<u># of Animals</u>		<u>Dose (mg/kg/day)</u>
	<u>M</u>	<u>F</u>	
C	50	50	Vehicle
LD	50	50	2.0
MD	50	50	20.0
HD	50	50	200.0

ORG 3770 was administered in the diet for 18 months followed by sacrifice and necropsy.

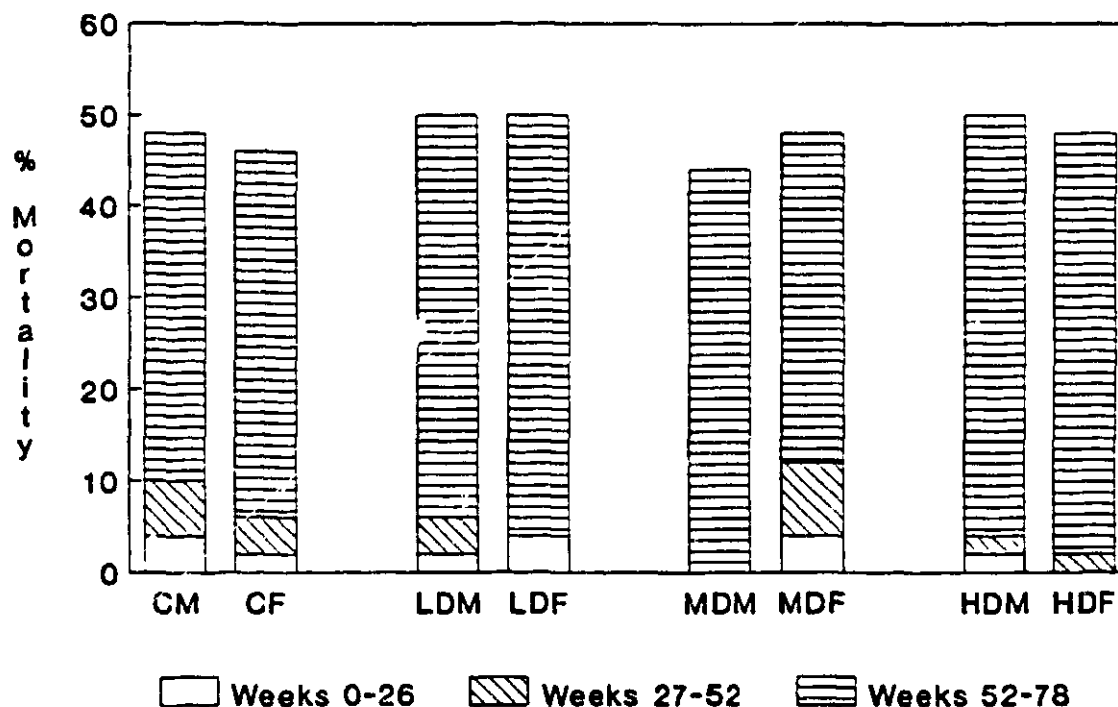
Observations:

Daily	Mortality and general behavior
Weekly	Physical examination
	Body weights
	Food consumption
Months 12 & 18	Blood smears (C & HD only)
Termination	Necropsy
	Organ weights
	Histopathology (C, HD and early decedent)
	Liver electron microscopy (12 HDM only)

Results:

1. Rates and causes of premature mortality are summarized in figure 1 and table 1, respectively. Eighteen month survival was at least 50% in all groups, and was not affected by treatment with ORG 3770. The most common cause of early death was chronic nephropathy, not an unusual finding in aged mice. The number of deaths due to hepatocellular carcinoma was increased from 2 in CM to 5 in HDM. There were no other changes in cause of death.
2. There were no behavioral indications of drug-related toxicity. A number of observations were common in all groups, especially late in the study, including excess lacrimation and chromodacryorrhea, yellow staining of the ano-genital region, alopecia and lens opacities. The number of animals with palpable tissue masses was not affected by ORG 3770 treatment.

Figure 1 - Premature Mortality



3. HDM body weights were decreased relative to CM by up to 4-6% at sporadic time points and at the end of the study (figure 2). Body weights in all other groups were unaffected. Food consumption was increased sporadically by up to 15% in MDM and HD animals. Drug intake was maintained within $\pm 20\%$ of targeted levels.
4. Differential WBC counts were similar in C and HD animals.
5. Gross necropsy indicated an increase in drug-treated males with liver masses or nodules (10, 10, 22 and 28% in C, LD, MD and HD, respectively). This finding was confirmed histopathologically by an increased incidence of hepatic adenoma and carcinoma in HDM (table 2). The sponsor attributes this finding to induction of hepatic microsomal enzyme activity, and cites a previous study in which ORG 3770 induced activities of cytochrome P₄₅₀, aminopyrine-N-demethylase, aniline

Table 1 - Causes of Death

		C	LD	MD	HD
Chronic nephropathy	♂	7	14	13	9
	♀	11	17	15	19
Hepatocellular carcinoma	♂	2	1	2	5
Malignant lymphoma	♂	1	0	1	1
	♀	1	1	2	0
Hemangiosarcoma	♂	0	1	0	0
	♀	1	0	0	0
Histiocytic sarcoma	♂	0	0	0	1
	♀	1	0	1	0
Cardiac septic thrombosis	♂	1	0	1	1
	♀	1	0	0	0
Other neoplastic ^a	♀	1	1	1	1
Other nonneoplastic	♂	4	1	3	2
	♀	0	2	0	2
Unknown	♂	9	8	2	6
	♀	7	4	5	2

^aIncludes one case each of hepatocellular adenoma, mammary carcinoma, endometrial sarcoma and granulocytic leukemia

hydroxylase and several other hepatic enzymes. Examination of animals not bearing hepatic tumors did indicate an increase in hepatic vacuolation (10, 12, 17 and 13/50 in CM, LDM, MDM and HDM), possibly due to induction. However, comparison of electron photomicrographs of livers from 3 CM and 3 HDM revealed no ultrastructural differences between the two treatment groups. There were no other significant changes in the incidence of neoplasms.

The most frequent nonneoplastic findings included amyloidosis of the heart, spleen, adrenals, liver and GI tract, chronic pneumonia, mesenteric congestion and lymphoid hyperplasia, chronic nephropathy, testicular degeneration and uterine endometrial hyperplasia. None of these appeared to be affected by ORG 3770 treatment, but instead were consistent with age-related findings in this species. The sponsor's histopathology summary tables are included as an appendix to this review.

Figure 2 - Body Weights

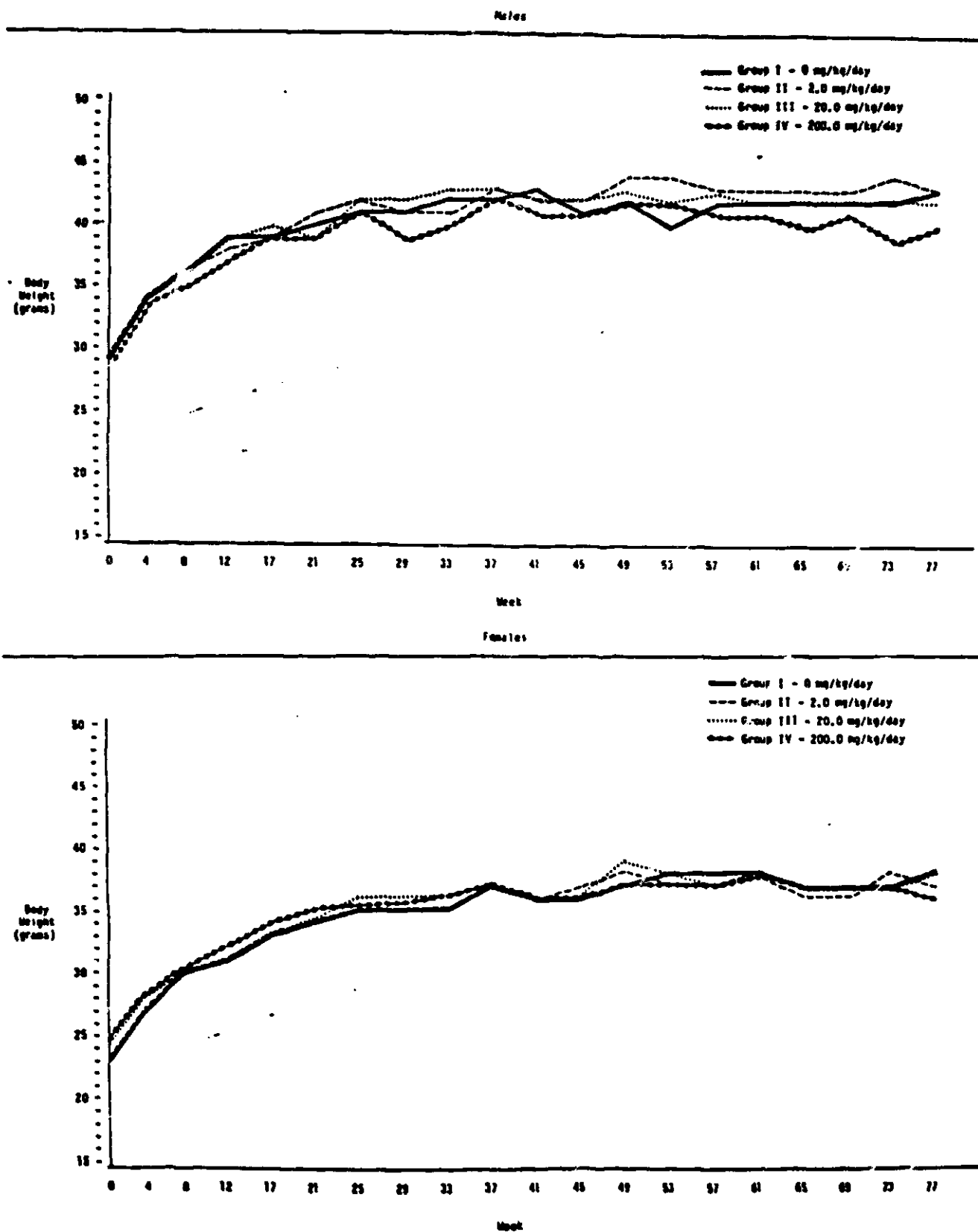


Table 2 - Neoplastic Findings

		C	LD	MD	HD
Hepatic adenoma	♂	3	3	6	10 ^a
	♀	1	2	1	0
Hepatic carcinoma	♂	4	2	5	8
	♀	0	0	0	1
Hepatic hemangioma/sarcoma	♂	1	3	1	0
	♀	3	2	1	0
Lung carcinoma/adenoma	♂	4	3	1	2
	♀	3	0	0	4
Malignant lymphoma	♂	1	0	1	1
	♀	3	1	2	2
Granulocytic leukemia	♀	0	0	0	1
Histiocytic sarcoma	♂	0	0	0	1
	♀	1	0	1	0
Testicular interstitial cell tumor	♂	0	1	1	0
Mammary carcinoma	♀	0	0	1	0
Ovarian cystadenoma	♀	0	1	1	0
Uterine sarcoma/leiomyoma	♀	2	1	1	1
Endometrial stromal polyps	♀	1	0	2	3
Other	♂	1	1	3	0
	♀	1	2	0	2

^ap<.05 vs. control (Fisher)

B. A 24 month feeding study in rats with ORG 3770 .

J)

A total of 400 Sprague-Dawley CD rats were subdivided into the following groups:

Group	# of Animals		Dose (mg/kg/day)
	M	F	
C	50	50	Vehicle
LD	50	50	2
MD	50	50	20
HD	50	50	60

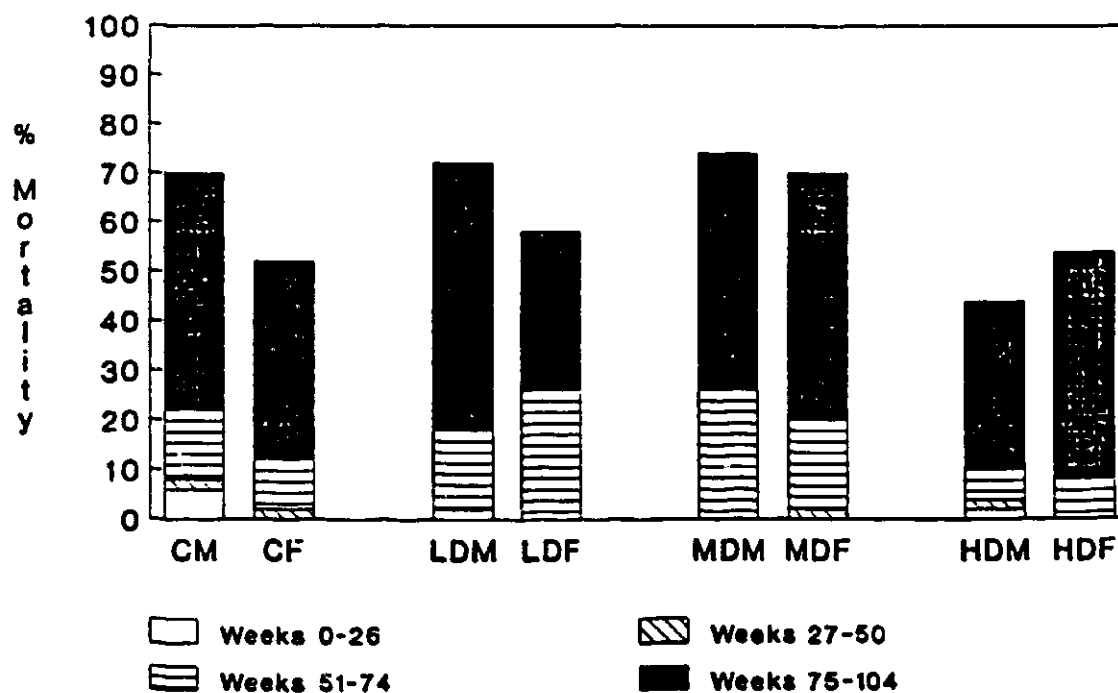
ORG 3770 (batch P) was administered in the diet for 24 months followed by sacrifice and necropsy.

Observations:

Daily	Mortality and general behavior
Weekly	Physical examination
	Body weights
	Food consumption
Months 12, 18 & 24	Blood smears (C & HD only)
Termination	Necropsy
	Organ weights
	Histopathology (C, HD and early decedents)

Results:

Figure 3 - Premature Mortality



1. Rates of premature mortality are summarized in figure 3. Overall 18 month survival ranged from 74-92% but 24 month survival was considerably lower (30-56%). Early deaths were increased in MDF (70% vs. 52% in CF, $p < .05$) but were decreased in HDM (44% vs. 70% in CM, $p < .01$). Individual causes of deaths were not provided for premature decedents.
2. The sponsor reported no behavioral observations indicative of drug-related toxicity. A number of findings including chromodacryorrhea, excessive lacrimation and sores of the skin, tail and ears were observed in all groups, including controls.
3. Body weights were reduced by 8-39% in all drug treatment groups in a dose-related manner (figure 4).
4. Food consumption was comparable in all groups except for HDF, in which there were 5-30% increases. Drug consumption was generally maintained within 10% of target doses (range -20 to +57%). However, analysis of ORG 3770 content in the diet revealed fairly large variations (up to 50%) in the distribution of drug in the diet material.
5. Total and differential WBC data from C and HD animals were unremarkable.
6. Tumor data are summarized in table 3. The sponsor's summary tables are also appended to this review. ORG 3770 treatment was associated with an increase in thyroid follicular adenomas in all treated male groups and an increase in liver adenomas in the MDF and HDF groups. The increase in thyroid tumors was dose-related and appeared to be accompanied by an increase in thyroid follicular carcinomas in HDM. C-cell tumor frequencies were not significantly increased. The sponsor suggests that changes in thyroid follicular tumor frequency may have been secondary to induction of hepatic P450, but does not provide supporting evidence such as measurement of hepatic enzyme or serum TSH levels. The increase in liver adenomas was evident only in females (MDF $p = 0.058$ and HDF $p = 0.028$ vs CF), and was not accompanied by changes in the frequency of other hepatic tumors (e.g. carcinoma). Although not statistically significant, there also appeared to be a general trend toward increased uterine neoplasms in the HDF group. Thus, there were increases in the frequency of uterine endometrial sarcomas (2 vs. 0), other uterine tumors (2 vs. 1) and uterine endometrial polyps (4 vs. 1), as well as cervical hyperplasia (2 vs. 0) in HDF vs. CF. The incidence of other neoplastic and nonneoplastic findings did not appear to be affected by ORG 3770. Total tumor counts and percentages of tumor bearing animals were also unaffected.

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Figure 4 - Body Weights

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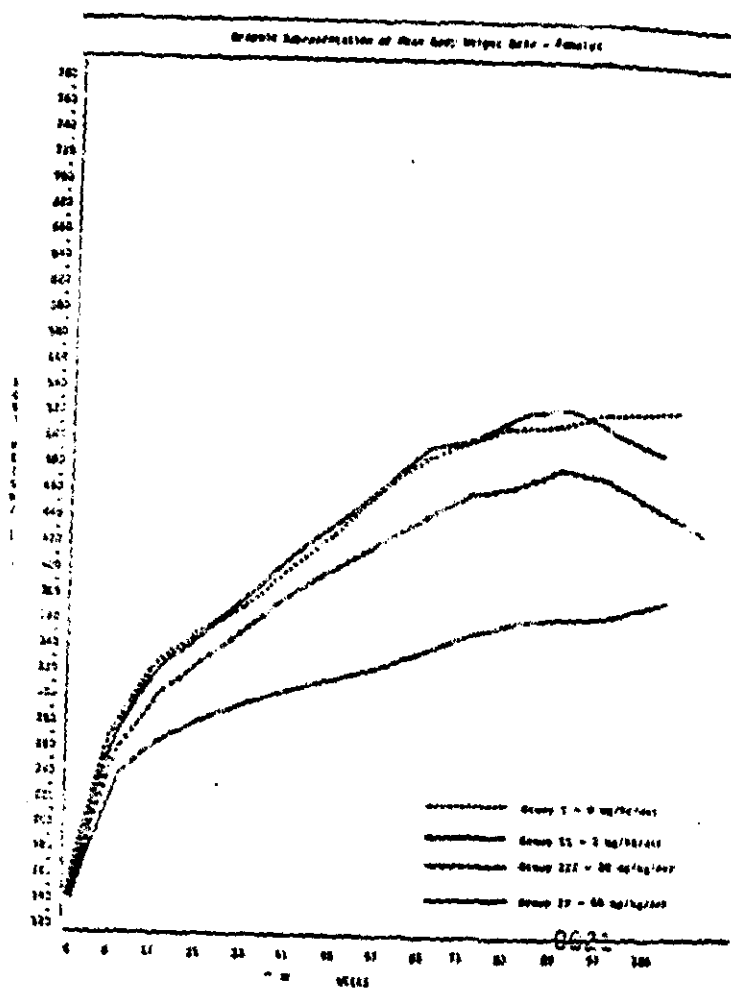
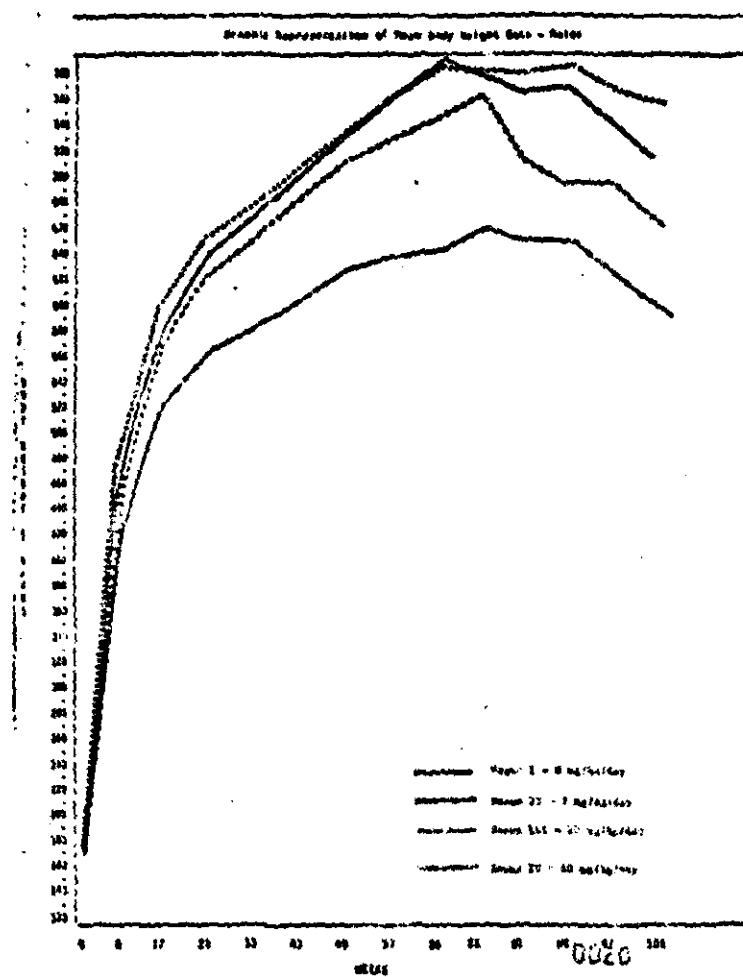


Table 3 - Neoplastic Findings

		C	LD	MD	HD
Hepatocellular adenoma	♂	0	0	0	3
	♀	0	0	4	5 ^a
Hepatocellular carcinoma	♂	1	1	1	3
	♀	1	0	0	1
Thyroid follicular adenoma	♂	1	4	5	9 ^a
	♀	1	1	1	1
Thyroid follicular carcinoma	♂	0	1	1	3
	♀	0	0	1	0
Thyroid C-cell adenoma	♂	5	3	7	7
	♀	2	7	2	3
Thyroid C-cell carcinoma	♂	0	0	1	0
	♀	0	1	1	0
Testicular interstitial cell tumor	♂	0	2	0	3
Uterine endometrial sarcoma	♀	0	0	0	2
Other uterine/ovarian tumors	♀	1	0	0	2
Uterine endometrial polyps	♀	1	0	3	4
Mammary fibroadenoma	♀	12	11	13	7
Mammary adenoma	♀	1	2	2	1
Mammary fibroma	♀	4	0	0	0
Mammary carcinoma	♂	0	2	0	0
	♀	14	13	13	19
Mammary fibrosarcoma	♂	1	0	0	1
	♀	1	0	1	0
Mammary lipoma	♂	0	0	0	0
	♀	1	0	1	0
Adrenal adenoma	♂	0	1	1	0
	♀	3	2	1	3
Adrenal carcinoma	♂	1	0	0	0
	♀	0	0	0	2

Table 3 (continued)

Pheochromocytoma	♂	4	6	7	2
	♀	1	2	0	3
Pancreatic islet cell adenoma	♂	4	1	2	2
	♀	2	1	3	1
Pituitary adenoma	♂	22	24	22	22
	♀	41	43	45	35
Pituitary carcinoma	♂	0	1	0	0
	♀	2	1	1	3
Renal lipoma	♂	0	1	1	0
	♀	0	0	0	1
Brain glioma	♂	0	2	0	2
	♀	0	0	0	1
Skin squamous cell papilloma	♂	4	3	3	2
	♀	2	1	0	1
Skin squamous cell carcinoma	♂	0	0	0	1
	♀	0	0	0	1
Skin fibroma/fibrosarcoma	♂	0	2	0	2
	♀	1	1	4	2
Histiocytic sarcoma	♂	2	2	0	0
	♀	0	0	2	0
Malignant lymphoma	♂	1	0	0	1
	♀	2	0	0	0
Granulocytic leukemia	♂	0	1	0	1
	♀	0	0	0	0
Other	♂	3	3	1	5
	♀	2	2	1	2
# Tumor-bearing animals	♂	34	39	36	37
	♀	47	47	48	48
Total tumor count	♀	70	93	52	87
	♀	104	96	115	113

*p<.05 (Fisher)

Summary and Evaluation

ORG 3770 is an antidepressant structurally related to mianserin. It has antagonist activity at serotonergic 5-HT₂ receptors and noradrenergic α_2 adrenoceptors. The present review covers the 2 carcinogenicity studies submitted by the sponsor, AKZO-Organon.

The mouse study was conducted in CD-1 mice at nominal dietary doses of 2 to 200 mg/kg. No data were submitted on the rationale for these doses (i.e. no ranging studies appear to have been performed) or for proof of absorption. The most significant finding was an increase in hepatic adenomas and carcinomas in males dosed with 200 mg/kg. There were 10 adenomas and 8 carcinomas in this group vs. 3 and 4, respectively in controls. Five of the HDM carcinomas led to premature deaths vs. 2 in the CM group. There were no significant changes in hepatic tumor incidences at lower doses in males or in any of the female groups, nor were there any significant changes in the incidence of other tumor types. The sponsor suggests that the liver tumors in HDM were secondary to hepatic microsomal enzyme induction, citing a previous study in mice in which ORG 3770 induced the activities of hepatic metabolizing enzymes. In addition, previous toxicity studies have generated evidence of hepatic induction in dogs (e.g. increased liver weights, changes in morphology). Although the present study failed to detect ultrastructural liver changes which would have confirmed induction, the small sample size (n=3) probably limited the power of this analysis.

The rat study utilized ORG 3770 doses of 2-60 mg/kg. Again, no rangefinding data appear to have been generated, but a one year dietary study indicated marked and progressive body weight loss and renal cytoplasmic vacuolation at 120 mg/kg. Significant findings in the carcinogenicity study included an increase in thyroid follicular adenomas in all treated male groups and an increase in liver adenomas in females at 20 and 60 mg/kg. Again these changes were suggested to be due to hepatic enzyme induction, although there is no direct evidence that this occurs in the rat. In addition, there appeared to be a trend toward elevated uterine tumors and increased cervical hyperplasia in females dosed with 60 mg/kg. Although not statistically significant, this could be indicative of an endocrine disturbance not previously detected.

Hepatic microsomal induction is an accepted nongenotoxic mechanism by which certain tumor types may be increased in animals. Thus, hepatic tumors may be induced in mice by known inducing agents (e.g. phenobarbital, benzodiazepines) and the background incidence of these tumors is high, at least in some strains (e.g. male B6C3F1 mice). Therefore, the mouse tumor data in the present study are not particularly disturbing for the following reasons: (1) mutagenicity studies indicate no direct ORG 3770 genotoxicity, (2) hepatic microsomal induction has been demonstrated in this and other species, and (3) the liver tumors were restricted to a single sex (males) and dosage group. Thus, regulatory action does not appear warranted on the basis of the mouse study.

The rat data also appear to fall under the same category, although the rationale is somewhat less clear cut. Increased thyroid follicular tumor incidence is a known effect of drug-induced hepatic induction in the rat. The accepted mechanism involves an increase in thyroxine (T₄) turnover, which leads to disinhibition of thyroid stimulating hormone (TSH) secretion. The resulting thyrotropic action of TSH may then lead to follicular tumorigenesis. This mechanism appears to be a possible basis for the dose-related increase in thyroid tumors observed in male rats dosed with ORG 3770. However, the sponsor has supplied little supporting evidence to indicate that this mechanism is operative for ORG 3770 administration in the rat. Thus no hepatic changes (e.g. organ weights, morphology, enzyme activities, etc.) have been reported in rats dosed with ORG 3770, nor has direct evidence of a neuroendocrine disturbance been furnished. Clearly, the sponsor's argument would be more convincing if one or both of the following was demonstrated: that similar ORG 3770 doses in rats result in elevation of hepatic weights, P450 content and/or enzyme activities, and that ORG 3770 administration reduces thyroxine or increases TSH levels. A neuroendocrine study including measurement of follicle stimulating hormone (FSH) and luteinizing hormone (LH) levels might

also provide additional evidence relating to the possible changes in uterine tumor frequency observed in females dosed with ORG 3770. I suggest that we ask the sponsor to supply such evidence before accepting the hepatic induction model as the basis for the observed changes in rat tumor frequencies.

Recommendations

The following should be communicated to the sponsor:

Please refer to your submissions to IND dated 6-27-89 and 6-13-90 containing the reports respectively entitled: "An eighteen month carcinogenicity feeding study in mice with ORG 3770" and "A twenty-four month feeding study in rats with ORG 3770" to which the following comments refer:

1. Future carcinogenicity studies should include a description of the rationale for dosage selection and proof of absorption (i.e. plasma drug levels), especially for dietary drug administration.
2. Although there appears to be good evidence that the observed increase in hepatic tumors in the mouse is related to microsomal induction, there is little direct evidence to support such a mechanism in the rat (i.e. little or no supporting data for the particular case of ORG 3770 in this species). Therefore, we request you to provide such data, in the form of evidence that similar dietary ORG 3770 doses in the rat result in elevation of hepatic weights, P450 content and/or enzyme activities, and/or that ORG 3770 administration reduces thyroxine levels or increases TSH levels. A neuroendocrine study including measurement of follicle stimulating hormone (FSH) and luteinizing hormone (LH) levels might also provide additional evidence relating to the possible changes in uterine tumor frequency and cervical hyperplasia observed in females dosed with ORG 3770 at 60 mg/kg. We would be amenable to consultation in the presentation of this data and/or the planning of any new studies.


Gary Evoniuk, Ph.D.

CC:
IND ORIG.
HFD-120

/JContrera
/GEvoniuk

 11/30/90

Appendix 1

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*** PATH/TON SYSTEM OUTPUT ***
AN EIGHTEEN MONTH CARCINOGENICITY FEEDING STUDY
IN MICE WITH ORG 3770
INCIDENCE SUMMARY

STUDY NUMBER: 052939

TABLE INCLUDES:									
SEX:MALE.....FEMALE.....									
GROUP: 1. 2. 3. 4. 1- 2- 3- 4.									
NUMBER OF ANIMALS AFFECTED									
ORGAN AND FINDING DESCRIPTION									
.. TOP OF LIST ..									
BRAIN (BN)	NUMBER EXAMINED:	50	25	22	50	50	50	50	50
CERVICAL SC (SC1)	NUMBER EXAMINED:	47	23	19	48	47	24	21	49
NERVE SCIATIC (NE1)	NUMBER EXAMINED:	47	24	20	45	45	23	22	49
HEART (HT)	NUMBER EXAMINED:	50	25	22	50	50	25	24	50
TRACHEA (TR)	NUMBER EXAMINED:	48	24	22	50	48	24	23	47
LUNGS (LU)	NUMBER EXAMINED:	50	30	24	50	50	25	25	50
..B-ALVEOLEGIC ADENOMA		0	0	0	1	1	0	0	4
..M-ALVEOLEGIC CARCINOMA		4	3	1	1	2	0	0	0
MESENTERIC LN (LN1)	NUMBER EXAMINED:	46	28	28	49	48	29	28	49
MEDIASTINAL LN (LN2)	NUMBER EXAMINED:	32	20	14	36	37	19	23	44
TITRUS (TR)	NUMBER EXAMINED:	37	18	15	44	47	21	20	47
SPLEEN (SP)	NUMBER EXAMINED:	50	28	23	50	49	29	26	50
BONE STERNUM (SO1)	NUMBER EXAMINED:	49	24	22	49	50	25	24	50
BONE FEMUR/JOINT (SO2)	NUMBER EXAMINED:	50	25	22	48	50	25	24	50
MARROW STERNUM (SO1)	NUMBER EXAMINED:	48	24	22	50	50	25	24	50
MARROW FEMUR (SO2)	NUMBER EXAMINED:	50	25	22	47	50	25	24	50
ESOPHAGUS (ES)	NUMBER EXAMINED:	49	25	22	50	50	25	24	50
LIVER (LI)	NUMBER EXAMINED:	50	50	50	50	49	32	30	50
..B-HEPATOCYLLULAR ADENOMA		3	3	6	10	1	2	1	0
..B-HEPATOCYLLULAR CARCINOMA		4	2	5	8	0	0	0	1
..M-HEPATOCYLLULAR CARCINOMA		1	1	1	0	3	0	1	0
..B-HEPATOCYLLULAR CARCINOMA		0	2	0	0	0	2	0	0
GALLBLADDER (GB)	NUMBER EXAMINED:	43	29	44	41	41	22	15	45

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*** PATH/TOX SYSTEM OUTPUT ***
AN EIGHTEEN MONTH CARCINOGENICITY FEEDING STUDY
IN MICE WITH ORG 3770
INCIDENCE SUMMARY

STUDY NUMBER: 852939

--- NUMBER OF ANIMALS AFFECTED ---

TABLE INCLUDES:

SEX=ALL; GROUP=ALL; SCREEN=ALL; WEEKS=ALL
DEATH=ALL; FIND=0, N, K; SUBSET=ALL

SEX: --- MALE --- FEMALE ---
GROUP: -1- -2- -3- -4- -1- -2- -3- -4-

NUMBER: 50 50 50 50 50 50 50 50

ORGAN AND FINDING DESCRIPTION

SALIVARY GLANDS (SG) NUMBER EXAMINED: 50 25 22 50 49 25 24 50

STOMACH (ST) NUMBER EXAMINED: 50 25 22 50 49 25 24 49

DUODENUM (DU) NUMBER EXAMINED: 47 21 22 49 46 24 22 47

PANCREAS (PA) NUMBER EXAMINED: 50 26 22 50 49 24 24 49
--N-HEMANGIOSARCOMA
0 1 0 0 0 0 0 0

JEJUNUM (JE) NUMBER EXAMINED: 47 22 20 48 46 24 22 47
--B-ADENOMA
0 0 1 0 0 0 0 0

ILEUM (IL) NUMBER EXAMINED: 44 19 20 48 47 24 21 47

CECUM (CE) NUMBER EXAMINED: 46 16 21 46 44 20 18 47

COLON (CO) NUMBER EXAMINED: 48 25 22 48 46 25 23 48

RECTUM (RC) NUMBER EXAMINED: 50 25 22 50 47 24 23 49

KIDNEYS (KD) NUMBER EXAMINED: 50 39 29 50 50 29 29 50

URINARY BLADDER (UB) NUMBER EXAMINED: 50 23 22 50 48 24 23 50

TESTES (TE) NUMBER EXAMINED: 50 25 24 49 0 0 0 0
--S-U/INTERSTITIAL CELL TUMOR
0 1 1 0 0 0 0 0

EPIDIDYMIDES (EP) NUMBER EXAMINED: 50 24 24 49 0 0 0 0

PROSTATE (PR) NUMBER EXAMINED: 50 25 22 50 0 0 0 0

SEMINAL VESICLES (SV) NUMBER EXAMINED: 50 34 30 50 0 0 0 0

OVARIES (OV) NUMBER EXAMINED: 0 0 0 0 49 39 38 50
--S-U/PAPILLARY CYSTADENOMA
0 0 0 0 0 1 1 0

UTERUS (UT) NUMBER EXAMINED: 0 0 0 0 49 38 36 50
--N-ENDOMETRIA; STROMAL SARCOMA
0 0 0 0 1 0 0 0
--S-LEIOMYOMA
0 0 0 0 1 1 1 1

*** CONTINUED ON NEXT PAGE ***

*** PATH/TOX SYSTEM OUTPUT ***
AN EIGHTEEN MONTH CARCINOGENICITY FEEDING STUDY
IN MICE WITH ORG 3770
INCIDENCE SUMMARY

STUDY NUMBER: 032939

... NUMBER OF ANIMALS AFFECTED ...

TABLE INCLUDES:	SEX:		MALE		FEMALE	
	GROUP:	1	2	3	4	5
DEATHS=ALL; FIND=B,N,M; SUBSET=ALL		1	2	3	4	5
SEX=ALL; GROUP=ALL; SCREEN=ALL; WEEKS=ALL		1	2	3	4	5
ORGAN AND FINDING DESCRIPTION		1	2	3	4	5
.. FROM PREVIOUS PAGE ..		1	2	3	4	5
UTERUS (UT)	NUMBER EXAMINED:	0	0	0	0	0
--B-ENDOMETRIAL STROMAL POLYP		0	0	0	0	0
--B-NEMANGIOMA		0	0	0	0	0
PITUITARY GLAND (PG)	NUMBER EXAMINED:	49	22	21	49	45
		24	25	23	49	49
THYROID GLAND (TH)	NUMBER EXAMINED:	48	23	22	50	46
--B-FOLLICULAR CELL ADENOMA		0	0	1	0	0
PARATHYROID GLS. (PT)	NUMBER EXAMINED:	26	9	9	27	23
--B-ADENOMA		0	0	0	1	0
ADRENAL GLANDS (AD)	NUMBER EXAMINED:	49	24	22	50	48
--M-U/PNECHROMOCYTOMA		0	0	0	0	0
--B-U/CORTICAL ADENOMA		1	0	0	0	0
ADRENAL CORTEX (AD1)	NUMBER EXAMINED:	0	0	0	0	0
ADRENAL MEDULLA (AD2)	NUMBER EXAMINED:	0	0	0	0	0
EYES (EY)	NUMBER EXAMINED:	49	31	32	50	49
MUSC BICEPS FEM (SM1)	NUMBER EXAMINED:	50	23	21	50	25
SKIN R ING (SK1)	NUMBER EXAMINED:	50	34	32	50	27
--M-FIBROSARCOMA		0	0	0	0	0
--B-SEBACEOUS CELL ADENOMA		0	0	1	0	0
MAMMARY R ING (MG1)	NUMBER EXAMINED:	9	2	1	8	47
--M-CARCINOMA		0	0	0	0	0
SPINAL CORD (SC)	NUMBER EXAMINED:	0	0	0	0	0
CAVITY (CA)	NUMBER EXAMINED:	0	0	0	0	0
SKIN (SK)	NUMBER EXAMINED:	0	0	0	0	1
GENERAL COMMENTS (GC)	NUMBER EXAMINED:	0	0	0	0	0

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*** PATH/TOX SYSTEM OUTPUT ***
AN EIGHTEEN MONTH CARCINOGENICITY FEEDING STUDY
IN MICE WITH ORG 3770
INCIDENCE SUMMARY

STUDY NUMBER: 852939

... NUMBER OF ANIMALS AFFECTED ...

TABLE INCLUDES:

SEX=ALL; GROUP=ALL; SCREEN=ALL; WEEKS=ALL
DEATH=ALL; FIND=B,N,X; SUBSET=ALL

SEX:MALE.....FEMALE.....
GROUP: -1- -2- -3- -4- -1- -2- -3- -4-

NUMBER: 50 50 50 50 50 50 50 50

ORGAN AND FINDING DESCRIPTION

LYMPH NODE (LN) NUMBER EXAMINED: 4 4 4 4 4 4 4 4

EARS (EA) NUMBER EXAMINED: 13 9 8 9 3 9 3 3

PENIS (PE) NUMBER EXAMINED: 4 1 3 0 0 0 0 0

SCROTUM (SO) NUMBER EXAMINED: 1 0 1 0 1 1 0 0

EXTREMITIES (EX) NUMBER EXAMINED: 1 0 2 0 1 0 1 1

TAIL (TA) NUMBER EXAMINED: 7 3 10 7 5 8 12 3

PREPUTIAL GLAND (PP) NUMBER EXAMINED: 1 2 4 1 0 0 0 0

MESENTERY (MS) NUMBER EXAMINED: 1 1 0 1 1 4 3 1

HARDERIAN GLANDS (HG) NUMBER EXAMINED: 1 0 0 1 0 1 0 0

..B-U/CYSTADENOMA NUMBER EXAMINED: 1 0 0 0 0 0 0 0

MAMMARY (MG) NUMBER EXAMINED: 0 0 0 0 0 0 0 0

MUSCLE (SM) NUMBER EXAMINED: 0 0 1 0 1 0 0 0

INCISORS (IN) NUMBER EXAMINED: 0 0 0 0 0 0 0 0

ADIPOSE TISSUE (AT) NUMBER EXAMINED: 0 0 0 0 0 0 0 0

LYMPHNODE, NEOPL (LN) NUMBER EXAMINED: 1 0 1 2 4 1 3 3

..N-MALIGNANT LYMPHOMA, NOS. NUMBER EXAMINED: 1 0 1 1 3 1 2 2

..N-HISTIOCYTIC SARCOMA NUMBER EXAMINED: 0 0 0 1 1 0 1 0

..N-MYELOSARCOMA/GRANULOCYTIC LEUKEMIA NUMBER EXAMINED: 0 0 0 0 0 0 0 1

GROSS/MICRO COR (G1) NUMBER EXAMINED: 0 0 0 0 0 0 0 0

GROSS/MICRO COR (G2) NUMBER EXAMINED: 0 0 0 0 0 0 0 0

.. END OF LIST ..



ORGANON Inc.

-1-

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Table IV A

**An Eighteen Month Carcinogenicity Feeding Study
in Mice with Org 3770
Pathology Report**

**Summary-Incidence of Histopathology Data
All Animals**

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*** PATH/TOX SYSTEM OUTPUT ***
AN EIGHTEEN MONTH CARCINOGENICITY FEEDING STUDY
IN MICE WITH ORG 3770
INCIDENCE SUMMARY

STUDY NUMBER: 852939

--- NUMBER OF ANIMALS AFFECTED ---

TABLE INCLUDED:
SEX=ALL; GROUP=ALL; SCREEN=ALL; WEEKS=ALL
DEATH=ALL; FIND=ALL; SUBSET=1

SEX: ---MALE--- FEMALE---
GROUP: 1. 2. 3. 4. 1. 2. 3. 4.

NUMBER: 50 50 50 50 50 50 50 50

NUMBER EXAMINED: 50 25 22 50 50 25 24 50

MINERALIZATION 4 0 1 0 1 0 0 2

ANUSSES(ES) 2 0 0 0 0 0 0 0

HEMORRHAGE 0 0 1 0 0 0 0 0

HEMORRHOES: LYMPHOID INFILTRATE 0 0 0 0 2 0 0 0

CERVICAL SC (SC1) 47 23 19 40 47 24 21 49

HEMORRHAGE 0 0 1 0 0 2 0 0

NERVE SCIATIC (NE1) 47 24 20 45 45 23 22 49

NEURITIS: METASTATIC NEOPLASM 0 0 0 0 0 1 0 0

HEART (HT) 50 25 22 50 50 25 24 50

CHRONIC MYOCARDITIS 1 0 0 0 0 0 0 0

NEURITIS: METASTATIC NEOPLASM 0 0 0 0 1 1 2 1

NEURITIS: SEPTIC THROMBUS 4 1 5 6 1 0 1 1

ANTILEIDOSIS 2 3 6 3 4 2 1 0

CHRONIC PERICARDITIS 0 0 0 0 1 0 1 1

ACUTE MYOCARDITIS 0 0 0 0 2 0 0 0

PERICARDITIS: MYOXA 0 0 1 0 0 0 0 0

ACUTE/SUBACUTE ENDOCARDITIS 1 2 0 0 0 2 0 0

OSSEOUS METAPLASIA 0 1 0 0 0 0 0 0

TRACHEA (TR) 48 24 22 50 48 24 23 47

NEURITIS: METASTATIC NEOPLASM 0 0 0 0 0 1 2 2

LUMEN: FREE BLOOD 1 0 0 0 0 0 0 0

LUNGS (LU) 50 30 24 50 50 25 25 50

CONGESTION 0 0 1 5 3 4 2 5

HEMORRHAGE 2 2 1 3 1 0 0 2

CHRONIC INTERSTITIAL PNEUMONIA 6 4 5 7 0 3 2 12

NEURITIS: METASTATIC NEOPLASM 0 0 1 1 1 1 2 1

ALVEOLOGENIC ADENOMA 0 0 0 1 1 0 0 4

GRANULOMA(S)/GRANULOMATOUS INFLAMMATION 1 0 0 0 0 0 0 0

INTRAVASCULAR LEUKOCYTOSIS 0 0 0 0 1 0 0 0

ACUTE INFLAMMATION 0 0 0 1 2 0 0 2

CHRONIC PLEURITIS 0 0 0 1 0 0 0 0

EDEMA 0 0 0 1 0 0 0 0

ATELECTASIS 0 1 0 1 1 0 0 0

CONTINUED ON NEXT PAGE **

STUDY NUMBER: 052939

ACUTE INFLAMMATION

CONTINUED ON NEXT PAGE

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*** PATH/TOX SYSTEM OUTPUT ***
AN EIGHTEEN MONTH CARCINOGENICITY FEEDING STUDY
IN NICE WITH ORG 3770
INCIDENCE SUMMARY

STUDY NUMBER: 052039

... NUMBER OF ANIMALS AFFECTED ...

TABLE INCLUDES:

SEX=ALL; GROUP=ALL; SCREEN=ALL; WEEKS=ALL
DEATH=ALL; FIND=ALL; SUBSET=1

SEX: MALE FEMALE
GROUP: 1. 2. 3. 4. 1. 2. 3. 4.

NUMBER: 50 50 50 50 50 50 50 50

ORGAN AND FINDING DESCRIPTION

.. FROM PREVIOUS PAGE ..

LIVER (LI) NUMBER EXAMINED: 50 50 50 50 50 50 50 50

--N-NEPHROSIS/AROSCH

--HEPATOCELLULAR HYPERTROPHY/HYPERPLASIA

--HEPATOCELLULAR VACUOLATION

--HEMATOCYST(S)

--SINUSOIDAL LEUKOCYTOSIS

--ABSCESS(ES)

--B-NEPHROSIS

--MULTILOCULAR CYST(S)

--GRANULOMA(S)/GRANULOMATOUS INFLAMMATION

--PERITONEUM: CHRONIC INFLAMMATION/ADHESIONS

--PERIORTAL LYMPHOID CELL ACCUMULATION

--EOSINOPHYLIC FOCUS/AREA OF CELLULAR ALTERATION

--CENTROLOBULAR HEPATOCELLULAR HYPERTROPHY

BALLBLADDER (GB) NUMBER EXAMINED: 43 29 44 41 41 22 15 45

--ACUTE INFLAMMATION

--ANYLOIBOSIS

--CHRONIC INFLAMMATION

--EDEMA

--LUMEN: DILATION

--S-METASTATIC NEOPLASIA

--LUMEN: CONCRETIONS

SALIVARY GLANDS (SG) NUMBER EXAMINED: 50 25 22 50 49 25 24 50

--S-METASTATIC NEOPLASIA

--ANYLOIBOSIS

--CHRONIC INFLAMMATION

--PERIARTERITIS MUCOSA

STOMACH (ST) NUMBER EXAMINED: 50 25 22 50 49 25 24 49

--S-METASTATIC NEOPLASIA

--FORESTOMACH: KERATINOUS CYST(S)

--ANYLOIBOSIS

--GLANDULAR MUCOSA: CYST(S)

--GLANDULAR MUCOSA: MINERALIZATION

--PERITONEUM: CHRONIC INFLAMMATION

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*** PATH/ION SYSTEM OUTPUT ***
AN EIGHTEEN MONTH CARCINOGENICITY FEEDING STUDY
IN MICE WITH ORG 3770
INCIDENCE SUMMARY

STUDY NUMBER: 852939

... NUMBER OF ANIMALS AFFECTED ...

TABLE INCLUDES:
SEX=ALL; GROUP=ALL; SCREEN=ALL; WEEKS=ALL
DEATH=ALL; FIND=ALL; SUBSET=Y

SEX: MALE FEMALE
GROUP: -1- -2- -3- -4- -1- -2- -3- -4-

NUMBER: 50 50 50 50 50 50 50 50

ORGAN AND FINDING DESCRIPTION

DUODENUM (DU) NUMBER EXAMINED: 47 21 22 49 46 24 22 47
--ANTYLOIDOSIS 15 11 16 17 21 19 11 31
--ACUTE INFLAMMATION 0 0 0 0 0 0 1 0
--NECROSIS 0 0 0 0 0 0 0 1
--MUCOSA: HYPERPLASIA 0 0 0 0 1 0 0 1
--ENTEROLITH 0 0 0 0 0 0 0 1

PANCREAS (PA) NUMBER EXAMINED: 50 26 22 50 49 24 24 49
--S-METASTATIC NEOPLASM 0 0 0 0 1 1 0 0
--H-HEMANGIOSARCOMA 0 1 0 0 0 0 0 0
--ADHESIONS TO ABDOMINAL WALL 0 0 0 0 0 0 0 1
--MESENTERY: ACUTE INFLAMMATION/NECROSIS 0 0 0 1 0 0 0 0
--CHRONIC INFLAMMATION/ACINAR ATROPHY 1 0 0 0 3 1 0 0
--PANCREATIC DUCT: DILATION/CTYSTS 0 0 0 0 1 0 0 0
--PANCREATIC DUCT: MINERAL DEPOSITION 0 1 0 0 0 0 0 0

JEJUNUM (JE) NUMBER EXAMINED: 47 22 20 48 46 24 22 47
--ANTYLOIDOSIS 20 16 17 25 25 20 16 31
--PERIARTERITIS NODOSA 0 0 0 0 0 0 0 0
--S-ADENOMA 0 0 1 0 0 0 0 0
--CHRONIC INFLAMMATION 1 0 0 0 0 0 0 0

ILEUM (IL) NUMBER EXAMINED: 44 19 20 48 47 24 21 47
--ANTYLOIDOSIS 27 16 19 30 28 21 17 36
--HEMORRAGE 0 0 1 0 0 0 0 0

CECUM (CE) NUMBER EXAMINED: 46 16 21 46 44 20 18 47
--SUBMUCOSAL EDEMA 1 1 4 3 0 1 2 5
--ACUTE INFLAMMATION 0 0 1 1 0 0 0 0
--S-METASTATIC NEOPLASM 0 0 1 1 0 0 0 0
--LUMEN: MENATODES 2 0 0 4 0 0 0 1
--LUMEN: FREE BLOOD 0 0 1 0 0 0 0 0
--LUMEN: RED FECAL MATERIAL 0 0 1 1 0 0 0 0

COLON (CO) NUMBER EXAMINED: 48 25 22 48 46 25 23 48
--S-METASTATIC NEOPLASM 0 0 0 1 1 0 0 0
--LUMEN: MENATODES 3 2 3 6 0 0 2 5
--LUMEN: DEEP RED FECAL MATERIAL 0 0 0 1 0 0 0 0

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*** PATH/TOX SYSTEM OUTPUT ***
AN EIGHTEEN MONTH CARCINOGENICITY FEEDING STUDY
IN MICE WITH ORG 3770
INCIDENCE SUMMARY

STUDY NUMBER: 852939

*** NUMBER OF ANIMALS AFFECTED ***

TABLE INCLUDES:
SEX=ALL; GROUP=ALL; SCREEN=ALL; WEEKS=ALL
DEATH=ALL; FIND=ALL; SUBSET=7

SEX: MALE FEMALE
GROUP: 1. 2. 3. 4. 1. 2. 3. 4.

ORGAN AND FINDING DESCRIPTION
NUMBER: 50 50 50 50 50 50 50 50

RECTUM (RC) NUMBER EXAMINED: 50 25 22 50 47 26 23 69
--LUMEN: NEUTROPHILS
--S: METASTATIC NEOPLASM
--LUMEN: FREE BLOOD

KIDNEYS (KD) NUMBER EXAMINED: 50 39 29 50 50 29 24 50
--U/CHRONIC NEPHROPATHY
--S/CHRONIC NEPHROPATHY
--S/ANYLIOIDOSIS
--U/HYDRONEPHROSIS

U/CHRONIC NEPHROPATHY
--U/CORTICIST(S)
--S/METASTATIC NEOPLASM
--U/NEOPLASM
--U/INFARCT
--U/PURULENT INFLAMMATION
--S/PURULENT INFLAMMATION
--S/CONGESTION
--S/PERIARTERITIS NODOSA
--S/UBMUCOSA PIGMENT DEPOSITS

URINARY BLADDER (UB) NUMBER EXAMINED: 50 23 22 50 48 26 23 50
--UROTHELIAL HYPERPLASIA
--LUMEN: PROTEINACEOUS PLUG
--LUMEN: DILATION
--S: METASTATIC NEOPLASM
--ACUTE/SUBACUTE INFLAMMATION
--UROTHELIUM: CYSTS
--NECROSIS
--LUMEN: SPERM
--CHRONIC INFLAMMATION

TESTES (TE) NUMBER EXAMINED: 50 25 24 49 0 0 0 0
--U/DEGENERATION OF GERMINAL EPITHELIUM
--S/DEGENERATION OF GERMINAL EPITHELIUM
--S/ANYLIOIDOSIS
--U/ACUTE INFLAMMATION
--U/SEMISPERMATOGENESIS
--U/SEMISPERMATOGENESIS: MINERALIZATION

*** CONTINUED ON NEXT PAGE ***

PRINTED: 00-JAN-88
PAGE: 8

*** PATH/TON SYSTEM OUTPUT ***
AN EIGHTEEN MONTH CARCINOGENICITY FEEDING STUDY
IN MICE WITH ORG 3770
INCIDENCE SUMMARY

STUDY NUMBER: 852939

--- NUMBER OF ANIMALS AFFECTED ---

TABLE INCLUDES:

SEX=ALL; GROUP=ALL; SCREEN=ALL; USERS=ALL
DEATH=ALL; FIND=ALL; SUBSET=Y

SEX: MALE FEMALE
GROUP: -1- -2- -3- -4- -1- -2- -3- -4-

NUMBER: 50 50 50 50 50 50 50 50 50 50

ORGAN AND FINDING DESCRIPTION

.. FROM PREVIOUS PAGE ..

TESTES (TE) NUMBER EXAMINED: 50 25 24 49 0 0 0 0 0 0

--B/SEMINIFEROUS TUBULES: MINERALIZATION

--U/SPERM CELL: ADENOMA

--B/HEMORRAGE

--U/NECROSIS

--B-U/INTERSTITIAL CELL TUMOR

EPIDIDYMIDES (EP) NUMBER EXAMINED: 50 24 24 49 0 0 0 0 0 0

--U/OLIGOSPERMIA

--B/OLIGOSPERMIA

--B/EPIDIDYMAL FAT PAD: ABSCESS

--B/HEMORRAGE

PROSTATE (PR) NUMBER EXAMINED: 50 25 22 50 0 0 0 0 0 0

--ACUTE INFLAMMATION

--ANTLOIDOSIS

--CHRONIC INFLAMMATION

SEMINAL VESICLES (SV) NUMBER EXAMINED: 50 34 30 50 0 0 0 0 0 0

--INCREASE IN SECRETORY MATERIAL

--ACUTE INFLAMMATION

--ABSCESS(ES)

OVARIES (OV) NUMBER EXAMINED: 0 0 0 0 49 39 38 50

--U/ANTLOIDOSIS

--B/ANTLOIDOSIS

--U/CYST(S)

--B/CYST(S)

--S-B/METASTATIC NEOPLASM

--U/NECROSIS

--B/NECROSIS

--B/MINERALIZATION

--B/PERIOVARIAN CHRONIC INFLAMMATION/FIBROSIS

--B-U/PAPILLARY CYSTADENOMA

UTERUS (UT) NUMBER EXAMINED: 0 0 0 0 49 38 36 50

--B-METASTATIC NEOPLASM

--NECROSIS

--HEMORRAGE

** CONTINUED ON NEXT PAGE **

PRINTED: 06-JAN-68
PAGE: 9

*** PATRIOT SYSTEM OUTPUT ***
AN EIGHTEEN MONTH CARCINOGENICITY FEEDING STUDY
IN MICE WITH ORG 3770
INCIDENCE SUMMARY

STUDY NUMBER: 052939

*** NUMBER OF ANIMALS AFFECTED ***

TABLE INCLUDES:
SEX=ALL; GROUP=ALL; SCREEN=ALL; WEEKS=ALL
DEATH=ALL; FIND=ALL; SUBSET=7

SEX: MALE FEMALE
GROUP: -1- -2- -3- -4- -1- -2- -3- -4-

ORGAN AND FINDING DESCRIPTION
NUMBER: 50 50 50 50 50 50 50 50 50 50

FROM PREVIOUS PAGE **

UTERUS (U): NUMBER EXAMINED: 49 22 21 49 45 24 23 50

--ENDOMETRIAL CYSTIC HYPERPLASIA 0 0 0 0 0 0 0 0 0 0

--H-ENDOMETRIAL STROMAL SARCOMA 0 0 0 0 0 0 0 0 0 0

--B-LEIOMYOMA 0 0 0 0 0 0 0 0 0 0

--B-ENDOMETRIAL STROMAL POLYP 0 0 0 0 0 0 0 0 0 0

--MENARCTOCYST(S) 0 0 0 0 0 0 0 0 0 0

--B-MENARCTOCYST(S) 0 0 0 0 0 0 0 0 0 0

--PERIARTERITIS MODOSA 0 0 0 0 0 0 0 0 0 0

--ENDOMETRIAL GLANDS: SQUAMOUS METAPLASIA 0 0 0 0 0 0 0 0 0 0

--LYMPHANGIOECTASIA 0 0 0 0 0 0 0 0 0 0

PITUITARY GLAND (PG) NUMBER EXAMINED: 49 22 21 49 45 24 23 50

--S-METASTATIC NEOPLASM 0 0 0 0 0 0 0 0 0 0

--PARS DISTALIS: CYST(S) 1 0 0 0 0 0 0 0 0 0

--PARS DISTALIS: HYPERPLASIA 0 0 0 0 0 0 0 0 0 0

THYROID GLAND (TH) NUMBER EXAMINED: 48 23 22 50 44 23 23 49

--FOLLICULAR CYST(S) 5 2 4 1 5 1 1 1 1 1

--ANTLOIDOSIS 2 4 4 3 17 6 3 13

--S-METASTATIC NEOPLASM 0 0 0 0 0 0 0 0 0 0

--B-FOLLICULAR CELL ADENOMA 0 0 0 0 0 0 0 0 0 0

--PERIARTERITIS MODOSA 0 0 0 0 0 0 0 0 0 0

--MENARCTOCYST(S) 0 0 0 0 0 0 0 0 0 0

PARATHYROID GLS. (PT) NUMBER EXAMINED: 24 9 9 27 23 16 16 33

--ANTLOIDOSIS 1 0 2 3 8 4 1 13

--B-ADENOMA 0 0 0 0 1 0 0 0 0 0

--LYMPHOID CELL INFILTRATE 0 0 0 0 0 0 0 0 0 0

ADRENAL GLANDS (AD) NUMBER EXAMINED: 49 24 22 50 48 25 24 50

--U/ANTLOIDOSIS 0 1 0 0 0 0 1 0 0 0

--B/ANTLOIDOSIS 24 17 19 28 24 21 15 31

--U/SUBCAPSULAR CELL REACTION 1 0 0 0 3 0 1 2

--B/SUBCAPSULAR CELL REACTION 4 1 0 0 27 0 9 8

--S-B/METASTATIC NEOPLASM 0 0 0 0 1 1 2 2

--U/ACCESSORY ADRENAL 1 2 0 0 4 3 3 1

--B/ACCESSORY ADRENAL 0 0 0 0 1 0 1 0 1

--U/ADHESIONS TO LIVER 0 0 0 0 1 0 0 0 0

--B/CONGESTION 0 1 0 0 0 0 0 1 0

** CONTINUED ON NEXT PAGE **

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PAGE: 10

*** PATH/TOX SYSTEM OUTPUT ***
AN EIGHTEEN MONTH CARCINOGENICITY FEEDING STUDY
IN MICE WITH DRG 1770
INCIDENCE SUMMARY

STUDY NUMBER: 852939

TABLE INCLUDES:

SEX=ALL;GROUP=ALL;SCREEN=ALL;WEERS=ALL
DEATH=ALL;FIND=ALL;SUBSET=1

SEX:MALE..... FEMALE.....
GROUP: -1- -2- -3- -4- -1- -2- -3- -4-

NUMBER: 50 50 50 50 50 50 50 50

ORGAN AND FINDING DESCRIPTION

.. FROM PREVIOUS PAGE ..

ADRENAL GLANDS (AD)

--M-U/NEOCHROMOCYTOMA

--U/NEOCHROMOCYTOMA

--B-U/ENDOCRINAL ADENOMA

--B/CONTEXT:HYPERPLASIA/HYPERPLASIA

--U/ACUTE INFLAMMATION

--B/EXTRAMEDULLARY HEMATOPOIESIS

EYES (EY)

--U/RETINAL ATROPHY

--U/ACUTE/SUBACUTE KERATITIS

--B/ACUTE/SUBACUTE KERATITIS

--U/PHTHISIS BULBI

--B/IRIS:MINERALIZATION

--U/ACUTE PANOPHTHALMITIS

--B/ACUTE PANOPHTHALMITIS

--S-U/METASTATIC NEOPLASM

--S-B/METASTATIC NEOPLASM

--U/CHRONIC KERATITIS/NEOVASCULARIZATION

--B/CHRONIC KERATITIS/NEOVASCULARIZATION

--U/LENS:DEGENERATION/SWELLING OF FIBERS

--U/MICROPHTHALMIA

--U/CORNEA:ENDOTHELIAL HYPERPLASIA

MUSC BICEPS FEM (SM)

--S-METASTATIC NEOPLASM

--ACUTE INFLAMMATION

SKIN RING (SK)

--SURFACE:DEBRIS

--HYPOTRICHOSIS

--SUBCUTIS:EDEMA

--ACUTE/SUBACUTE INFLAMMATION

--NECROSIS

--KERATINOUS CYST(S)

--S-METASTATIC NEOPLASM

--EPIDERMIS:HYPERPLASIA

--ABSCESSES

.. CONTINUED ON NEXT PAGE ..

AT
.....
NUMBER OF ANIMALS AFFECTED
.....
0546350 182800N 033200E

SEX:	MALE.....		FEMALE.....
GROUP: -1-	-2-	-3-	-4-

NUMBER: 50 50 50 50 50 50 50

100

ANIMED: 50 34 32 50 50 27 29 50

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ANIMEE: 9 2 1 8 47 25 23 50

5 4 0 5 0 0 0

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[illegible]

ANIMED: 0 0 0 0 0 0 0 0

REF: 6 6 4 4 4 4 4

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3
6
7

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SECRET

10203030

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22104021

0012000

STUDY NUMBER: 15-239

SECRET

CONFIDENTIAL

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PRINTED: 06-JAN-68
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*** PATH/TOX SYSTEM OUTPUT ***
AN EIGHTEEN MONTH CARCINOGENICITY FEEDING STUDY
IN MICE WITH ORG 3770
INCIDENCE SUMMARY

STUDY NUMBER: 852939

... NUMBER OF ANIMALS AFFECTED ...

TABLE INCLUDES:

SEX=ALL; GROUP=ALL; SCREEN=ALL; WEEKS=ALL
DEATH=ALL; FIND=ALL; SUBSET=Y

ORGAN AND FINDING DESCRIPTION

SEX: MALE FEMALE
GROUP: 1. 2. 3. 4. 1. 2. 3. 4.

NUMBER: 50 50 50 50 50 50 50 50

LYMPHOMET.NEOPL (LR) NUMBER EXAMINED: 1 0 1 2 4 1 3 3
--M-MALIGNANT LYMPHOMA, NOS.
--M-HISTIOCYTIC SARCOMA
--M-MYELOSARCOMA/GRANULOCYTIC LEUKEMIA
** END OF LIST **

Appendix 2

Table IV A

**A Twenty-four Month Feeding Study
in Rats with Org 3770
Pathology Report**

**Summary Incidence of Histopathology Data
All Animals**

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*** PATH/TOX SYSTEM OUTPUT ***
 A TWENTY-FOUR MONTH FEEDING STUDY
 IN RATS WITH ORG 3770
 INCIDENCE SUMMARY

PRINTED: 10-MAY-90
 PAGE: 2

STUDY NUMBER: 852938

--- NUMBER OF ANIMALS AFFECTED ---								
TABLE INCLUDES: SEX=ALL; GROUP=ALL; SCREEN=ALL; WEEKS=ALL DEATH=ALL; FIND=ALL; SUBSET=1	SEX: -----MALE-----				-----FEMALE-----			
	GROUP: -1-	-2-	-3-	-4-	-1-	-2-	-3-	-4-
ORGAN AND FINDING DESCRIPTION	NUMBER:	50	50	50	50	50	50	50
** TOP OF LIST **								
BRAIN (BN)	NUMBER EXAMINED:	50	36	37	50	50	30	35
--HYPOTHALAMUS: COMPRESSION		4	4	2	3	9	8	13
--N-GLIOMA		0	1	0	2	0	0	1
--N-GRANULAR CELL TUMOR		0	1	0	0	0	0	0
--HEMORRHAGE		1	2	2	0	3	4	3
--S-METASTATIC NEOPLASM		0	1	0	0	2	1	1
--VENTRICLES: DILATION		0	0	0	0	1	0	1
SPIN CORD (CERV) (SC)	NUMBER EXAMINED:	48	34	37	47	49	29	35
NERVE (SCIATIC) (NE)	NUMBER EXAMINED:	50	36	36	49	50	29	35
--ARTERIES: MINERALIZATION		1	0	0	0	0	0	0
HEART (HT)	NUMBER EXAMINED:	50	36	37	50	50	30	35
--CHRONIC MYOCARDITIS/FIBROSIS		11	11	4	9	4	3	1
--ATRIUM/AURICLE: THROMBUS		1	1	3	0	2	1	0
--VENTRICLE: THROMBUS		2	0	0	0	0	0	1
--CORONARY ARTERIES: MINERALIZATION		4	6	3	0	4	1	0
--MYOCARDIUM: MINERALIZATION		3	7	2	0	4	1	0
--S-METASTATIC NEOPLASM		1	1	0	1	0	0	0
--ACUTE ENDOCARDITIS		0	1	0	0	0	0	1
--HEMORRHAGE		0	1	0	0	0	0	0
--CONGESTION		1	0	0	0	0	0	0
--ACUTE PERICARDITIS		1	0	0	0	0	0	0
--CHRONIC PERICARDITIS		0	0	1	0	0	0	0
--N-MYXOMA		0	0	0	0	1	0	0
--ACUTE MYOCARDITIS		0	0	0	0	0	0	1
ESOPHAGUS (ES)	NUMBER EXAMINED:	50	35	37	49	50	29	35
--S-METASTATIC NEOPLASM		2	0	0	0	0	0	0
--LUMEN: FOREIGN MATERIAL/CELL DEBRIS		1	0	0	0	0	0	1
--LUMEN: DILATION		0	0	0	0	1	0	0
TRACHEA (TR)	NUMBER EXAMINED:	50	35	37	49	50	29	35
--S-METASTATIC NEOPLASM		2	0	0	0	0	0	0
LUNGS (LU)	NUMBER EXAMINED:	50	38	47	49	50	39	44
--CHRONIC INTERSTITIAL PNEUMONIA		29	24	33	31	29	25	22
--GRANULOMA(S)/GRANULOMATOUS INFLAMMATION		0	0	1	2	3	1	0

** CONTINUED ON NEXT PAGE **

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*** PATH/TOX SYSTEM OUTPUT ***
A TWENTY-FOUR MONTH FEEDING STUDY
IN RATS WITH ORG 3770
INCIDENCE SUMMARY

PRINTED: 10-MAY-90
PAGE: 6

STUDY NUMBER: B52938

TABLE INCLUDES:

SEX=ALL; GROUP=ALL; SCREEN=ALL; WEEKS=ALL
DEATH=ALL; FIND=ALL; SUBSET=T

--- NUMBER OF ANIMALS AFFECTED ---

ORGAN AND FINDING DESCRIPTION	SEX: -----MALE-----				-----FEMALE-----			
	GROUP: -1- -2- -3- -4-				-1- -2- -3- -4-			
	NUMBER:	50	50	50	50	50	50	50
THYMUS (TM) NUMBER EXAMINED:	41	24	28	40	42	21	29	30
-- INVOLUTION/ATROPHY	27	15	26	28	26	17	16	14
-- S-METASTATIC NEOPLASM	1	1	0	1	0	0	0	0
-- CONGESTION/HEMORRHAGE	2	2	2	0	0	0	0	1
-- CYST(S)	0	0	0	1	7	0	8	8
-- M-THYMOMA	0	0	0	0	0	0	0	1
-- LYMPHOID CELL HYPERPLASIA	0	0	0	2	1	0	0	0
-- EPITHELIAL HYPERPLASIA	0	0	0	0	0	0	0	1
SPLEEN (SP) NUMBER EXAMINED:	50	36	39	50	50	31	37	50
-- LYMPHOID CELL HYPERPLASIA	2	2	1	0	1	0	0	0
-- CONGESTION/HEMORRHAGE	2	2	2	1	1	1	0	1
-- RETICULOENDOTHELIAL CELLS: BROWN PIGMENT	10	11	5	8	25	19	15	25
-- EXTRAMEDULLARY HEMATOPOIESIS	11	11	4	4	11	4	10	9
-- S-METASTATIC NEOPLASM	2	1	0	1	0	1	1	0
-- RETICULOENDOTHELIAL CELL HYPERPLASIA	1	0	0	0	0	0	0	0
-- LYMPHOID CELL DEPLETION	0	0	0	1	0	1	0	0
-- STEATOSIS	0	0	0	0	0	1	0	0
BONE STERNUM (BO1) NUMBER EXAMINED:	50	36	36	50	50	27	33	50
-- OSSEOUS HYPERPLASIA	0	0	0	0	1	0	0	0
-- MYELOFIBROSIS	0	1	0	0	0	0	0	0
BONE FEMUR (BO2) NUMBER EXAMINED:	49	35	36	48	49	29	35	48
-- OSSEOUS HYPERPLASIA	0	1	0	0	1	0	0	0
-- MYELOFIBROSIS	0	2	5	0	0	0	0	0
MARROW STERNUM (BM1) NUMBER EXAMINED:	50	36	36	49	50	27	33	50
-- ERYTHROID/MYELOID CELL HYPERPLASIA	8	3	2	3	3	2	2	5
-- ERYTHROID/MYELOID CELL DEPLETION	0	0	0	0	3	1	0	0
-- S-METASTATIC NEOPLASM	0	2	0	2	0	0	0	0
-- CONGESTION/HEMORRHAGE	1	0	0	0	0	0	0	0
-- MYELOFIBROSIS	0	1	0	0	0	0	0	0
MARROW FEMUR (BM2) NUMBER EXAMINED:	49	35	36	46	49	29	35	48
-- ERYTHROID/MYELOID CELL HYPERPLASIA	7	3	2	3	3	2	2	5
-- ERYTHROID/MYELOID CELL DEPLETION	0	0	0	1	4	1	0	1
-- S-METASTATIC NEOPLASM	0	2	0	2	0	0	0	0
-- CONGESTION/HEMORRHAGE	1	0	0	0	0	0	0	0

** CONTINUED ON NEXT PAGE **

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*** PATH/TOX SYSTEM OUTPUT ***
 A TWENTY-FOUR MONTH FEEDING STUDY
 IN RATS WITH ORG 3770
 INCIDENCE SUMMARY

PRINTED: 10-MAY-90
 PAGE: 5

STUDY NUMBER: 852938

TABLE INCLUDES:

SEX=ALL; GROUP=ALL; SCREEN=ALL; WEEKS=ALL
 DEATH=ALL; FIND=ALL; SUBSET=1

--- NUMBER OF ANIMALS AFFECTED ---

ORGAN AND FINDING DESCRIPTION

** FROM PREVIOUS PAGE **

MARROW FEMUR (BM2) NUMBER EXAMINED: 49 35 36 46 49 29 35 48
 --MYELOFIBROSIS 0 4 4 1 0 0 0 0

LIVER (LI) NUMBER EXAMINED: 50 50 50 50 50 50 50 50

--B-NEPATOCELLULAR ADENOMA 0 0 0 3 0 0 4 5
 --H-NEPATOCELLULAR CARCINOMA 1 1 1 3 1 0 0 1
 --NEPATOCELLULAR VACUOLATION/VESICULATION 12 11 12 15 14 15 11 12
 --CONGESTION 19 14 20 8 9 10 9 10
 --TENSION LIPIDOSIS 6 1 2 4 6 8 9 5
 --SPONGIOSIS HEPATIS 9 15 10 23 0 0 1 4
 --BASOPHILIC FOCI/AREAS OF CELLULAR ALTERATION 4 4 1 8 3 1 1 4
 --EOSINOPHILIC FOCI/AREAS OF CELLULAR ALTERATION 2 5 8 14 3 1 9 7
 --CLEAR CELL FOCI/AREAS OF CELLULAR ALTERATION 0 0 0 1 0 1 0 0
 --INTRANEPTIC BILE DUCTS: HYPERPLASIA/SCLEROSIS 6 5 2 0 5 7 1 2
 --COAGULATIVE NECROSIS 3 3 6 4 9 7 7 3
 --ACUTE/SUBACUTE INFLAMMATION 2 0 0 0 0 3 2 3
 --PERIARTERITIS NODOSA 1 0 0 1 0 0 0 0
 --S-METASTATIC NEOPLASM 2 3 0 2 0 1 1 1
 --PELIOSIS HEPATIS 2 2 2 1 1 1 1 1
 --PERIportal LYMPHOID CELL ACCUMULATION 1 0 0 0 1 1 0 0
 --NEPATOCELLULAR HYPERTROPHY 1 0 0 1 1 0 1 5
 --NEPATOCELLULAR HYPERPLASIA 0 0 1 0 0 0 0 0
 --BILIARY CYSTS 0 1 2 3 4 0 4 2
 --HEMATOMA 0 0 0 0 0 0 0 1
 --CENTROLOBULAR HYPERTROPHY 0 0 0 0 0 0 0 1

SALIVARY GLANDS (SG) NUMBER EXAMINED: 50 35 37 50 49 28 33 50

--CHRONIC INFLAMMATION 0 1 0 0 0 0 0 0
 --S-METASTATIC NEOPLASM 0 1 0 0 0 0 0 0

STOMACH (ST) NUMBER EXAMINED: 50 41 40 50 50 35 39 50

--GLANDULAR MUCOSA: ACUTE INFLAMMATION/NECROSIS 2 4 0 1 5 3 0 2
 --FORESTOMACH: ULCER 2 3 0 0 0 2 1 0
 --GLANDULAR MUCOSA: CYSTS 5 2 2 1 3 0 0 2
 --FORESTOMACH: ACUTE INFLAMMATION 2 2 1 1 1 2 3 3
 --FORESTOMACH, S-MUCOSA: EDEMA 1 0 0 0 1 0 1 0
 --GLANDULAR MUCOSA/MUSCULARIS: MINERALIZATION 6 9 9 2 5 0 0 0
 --FORESTOMACH: SQUAMOUS CELL HYPERPLASIA 0 2 3 1 0 4 3 1
 --FORESTOMACH, MUCOSA: HYPERKERATOSIS 0 0 1 0 0 1 0 0

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*** PATH/TOX SYSTEM OUTPUT ***
 A TWENTY-FOUR MONTH FEEDING STUDY
 IN RATS WITH ORG 37/0
 INCIDENCE SUMMARY

PRINTED: 10-MAY-90
 PAGE: 6

STUDY NUMBER: 852938

TABLE INCLUDES:

SEX=ALL; GROUP=ALL; SCREEN=ALL; WEEKS=ALL
 DEATH=ALL; FIND=ALL; SUBSET=1

--- NUMBER OF ANIMALS AFFECTED ---

ORGAN AND FINDING DESCRIPTION	SEX: -----MALE-----				-----FEMALE-----			
	GROUP: -1-	-2-	-3-	-4-	-1-	-2-	-3-	-4-
NUMBER:	50	50	50	50	50	50	50	50
** FROM PREVIOUS PAGE **								
STOMACH (ST)	NUMBER EXAMINED:	50	41	40	50	50	35	50
--S-METASTATIC NEOPLASM		0	1	0	0	0	0	1
--PERIARTERITIS NODOSA		0	1	0	0	0	1	0
--KERATINOUS CYST(S)		0	0	1	0	0	0	0
DUODENUM (DU)	NUMBER EXAMINED:	47	37	37	48	49	30	49
--ACUTE INFLAMMATION/NECROSIS		0	0	0	0	0	1	0
--HEMORRHAGE		0	0	0	0	0	1	0
--PERIARTERITIS NODOSA		0	0	0	0	0	1	0
PANCREAS (PA)	NUMBER EXAMINED:	50	39	38	49	50	30	35
--ACINAR ATROPHY		1	5	2	10	8	3	3
--ISLET CELL HYPERPLASIA		2	1	0	1	0	0	0
--B-ISLET CELL ADENOMA		4	1	2	2	2	1	3
--H-ISLET CELL CARCINOMA		0	0	0	0	0	1	0
--PERIARTERITIS NODOSA		4	5	1	1	1	2	1
--STEATOSIS		3	5	10	10	3	3	1
--S-METASTATIC NEOPLASM		1	1	0	0	0	0	1
--MESENTERIC ARTERY THROMBOSIS		1	2	0	0	0	0	0
--MESENTERIC ARTERIES MINERALIZATION		0	1	0	0	0	0	0
--ACINAR HYPERPLASIA		0	0	0	1	0	0	0
--NECROSIS/HEMORRHAGE		0	0	1	0	0	0	0
JEJUNUM (JE)	NUMBER EXAMINED:	43	34	36	45	46	31	34
--CONGESTION		1	0	0	0	0	0	0
--LUMEN: NEMATODES		1	0	0	0	0	0	1
--ACUTE INFLAMMATION		1	0	1	0	0	0	0
--H-LEIOMYOSARCOMA		0	0	1	0	0	0	0
ILEUM (IL)	NUMBER EXAMINED:	37	28	24	42	43	25	29
--ACUTE INFLAMMATION		1	0	0	0	1	0	0
--LUMEN: NEMATODES		0	1	0	0	0	0	1
--LUMEN: INFLAMMATORY CELLS/DEBRIS		0	0	0	0	1	0	0
CECUM (CE)	NUMBER EXAMINED:	40	31	36	43	44	26	34
--ACUTE INFLAMMATION		3	0	2	1	3	0	1
--SUBMUCOSA: EDEMA		1	1	1	1	2	0	1
--NECROSIS		1	0	1	0	0	0	0
--LUMEN: NEMATODES		1	0	1	0	0	0	0

** CONTINUED ON NEXT PAGE **

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*** PATH/TOX SYSTEM OUTPUT ***
 A TWENTY-FOUR MONTH FEEDING STUDY
 IN RATS WITH DRG 3770
 INCIDENCE SUMMARY

PRINTED: 10-MAY-90
 PAGE: 7

STUDY NUMBER: 852938

--- NUMBER OF ANIMALS AFFECTED ---								
SEX: -----MALE----- FEMALE-----								
GROUP: -1- -2- -3- -4- -1- -2- -3- -4-								
ORGAN AND FINDING DESCRIPTION	NUMBER:	50	50	50	50	50	50	50

** FROM PREVIOUS PAGE **								
CECUM (CE)	NUMBER EXAMINED:	40	31	36	43	44	26	34
--GRANULOMATOUS INFLAMMATION		0	0	0	0	0	0	1
--HEMORRHAGE		1	0	1	0	0	0	0
COLON (CO)	NUMBER EXAMINED:	48	37	36	47	49	28	35
--LUMEN:NEMATODES		2	3	2	1	6	2	0
--MUSCULARIS:STEATOSIS		6	1	2	0	3	1	0
--S-METASTATIC NEOPLASM		1	0	0	0	0	0	1
--ACUTE INFLAMMATION		1	0	1	0	1	0	0
--NECROSIS		1	0	0	0	0	0	0
--HEMORRHAGE		1	0	0	0	0	0	0
RECTUM (RC)	NUMBER EXAMINED:	44	30	34	46	47	29	35
--LUMEN:NEMATODES		9	0	0	6	5	2	0
--ACUTE INFLAMMATION		2	0	1	0	1	0	0
--SUBMUCOSA:EDEMA		1	0	0	0	0	0	0
--S-METASTATIC NEOPLASM		1	0	0	0	0	0	1
--NECROSIS		1	0	0	0	0	0	0
--HEMORRHAGE		1	0	0	0	0	0	0
--MUCOSA:EOSINOPHILIC MATERIAL/CELLULAR DEBRIS		0	0	0	0	1	0	0
KIDNEYS (KD)	NUMBER EXAMINED:	50	43	43	49	50	38	41
--U/CHRONIC NEPHROPATHY		1	0	0	0	0	0	0
--B/CHRONIC NEPHROPATHY		43	39	39	45	35	31	29
--U/HYDRONEPHROSIS		2	0	1	2	2	0	2
--B/HYDRONEPHROSIS		4	5	2	2	4	5	4
--U/PELVIS:UROLITHS		2	2	2	3	6	7	4
--B/PELVES:UROLITHS		2	6	4	1	22	19	12
--U/UROTHELIUM:HYPERPLASIA		0	0	0	1	2	0	0
--B/UROTHELIUM:HYPERPLASIA		2	1	0	1	2	0	1
--U/CORTX:CYSTS		1	2	0	5	0	1	1
--B/CORTX:CYSTS		2	5	5	4	2	2	1
--B/CONGESTION		7	7	8	5	4	5	6
--B/CONVOLUTED TUBULAR EPITHELIUM:EOSINOPHILC DROPLETS		2	2	0	0	0	0	1
--B/CORTX:MINERALIZATION		6	5	3	2	5	1	0
--U/ACUTE/SUBACUTE PYELONEPHRITIS		0	0	1	0	0	0	1
--B/ACUTE/SUBACUTE PYELONEPHRITIS		5	1	3	3	0	0	1
--B/TUBULAR EPITHELIUM:BROWN PIGMENT		1	0	0	0	0	0	0
--S-B/METASTATIC NEOPLASM		0	2	0	1	0	1	0

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*** PATH/TOX SYSTEM OUTPUT ***
A TWENTY-FOUR MONTH FEEDING STUDY
IN RATS WITH ORG 3770
INCIDENCE SUMMARY

STUDY NUMBER: 852938

--- NUMBER OF ANIMALS AFFECTED ---

TABLE INCLUDES:

SEX=ALL; GROUP=ALL; SCREEN=ALL; WEEKS=ALL
DEATH=ALL; FIND=ALL; SUBSET=1

SEX: MALE FEMALE
GROUP: 1- 2- 3- 4- 1- 2- 3- 4-

NUMBER: 50 50 50 50 50 50 50 50

ORGAN AND FINDING DESCRIPTION

FROM PREVIOUS PAGE **

NUMBER EXAMINED: 50

50 50 50 50 50 50

EPIDIDYMIDES (EP)

NUMBER EXAMINED: 50

50 50 50 50 50 50

--S-B/METASTATIC NEOPLASIA

NUMBER EXAMINED: 49

49 49 49 49 49 49

PROSTATE (PR)

NUMBER EXAMINED: 10

10 10 10 10 10 10

--ACUTE/SUBACUTE INFLAMMATION

NUMBER EXAMINED: 1

1 1 1 1 1 1

--EPITHELIAL HYPERPLASIA

NUMBER EXAMINED: 0

0 0 0 0 0 0

--CHRONIC INFLAMMATION

NUMBER EXAMINED: 49

49 49 49 49 49 49

SEMINAL VESICLES (SV)

NUMBER EXAMINED: 4

4 4 4 4 4 4

--ACUMULATION OF SECRETORY MATERIAL

NUMBER EXAMINED: 0

0 0 0 0 0 0

--DECREASE OF SECRETORY MATERIAL

NUMBER EXAMINED: 0

0 0 0 0 0 0

--ACUTE/SUBACUTE INFLAMMATION

NUMBER EXAMINED: 0

0 0 0 0 0 0

OVARIES (OV)

NUMBER EXAMINED: 0

0 0 0 0 0 0

--U/CYST(S)

NUMBER EXAMINED: 0

0 0 0 0 0 0

--B-U/GRANULOSA/THECA CELL TUMOR

NUMBER EXAMINED: 0

0 0 0 0 0 0

--B/CONGESTION

NUMBER EXAMINED: 0

0 0 0 0 0 0

--S-B/METASTATIC NEOPLASIA

NUMBER EXAMINED: 0

0 0 0 0 0 0

--U/NEPHATOCYST

NUMBER EXAMINED: 0

0 0 0 0 0 0

UTERUS (UT)

NUMBER EXAMINED: 0

0 0 0 0 0 0

--ENDOMETRIAL CYST(S)

NUMBER EXAMINED: 0

0 0 0 0 0 0

--LUMEN DILATION

NUMBER EXAMINED: 0

0 0 0 0 0 0

--ADENOMATOSIS

NUMBER EXAMINED: 0

0 0 0 0 0 0

--S-METASTATIC NEOPLASIA

NUMBER EXAMINED: 0

0 0 0 0 0 0

--N-ENDOMETRIAL SQUAMOUS SARCOMA

NUMBER EXAMINED: 0

0 0 0 0 0 0

--ACUTE INFLAMMATION/NECROSIS

NUMBER EXAMINED: 0

0 0 0 0 0 0

--B-ENDOMETRIAL POLYP

NUMBER EXAMINED: 0

0 0 0 0 0 0

--B-ENDOMETRIAL ADENOMA

NUMBER EXAMINED: 0

0 0 0 0 0 0

--CERVIX: SQUAMOUS CELL HYPERPLASIA

NUMBER EXAMINED: 0

0 0 0 0 0 0

--B-ELONGATA

NUMBER EXAMINED: 0

0 0 0 0 0 0

--CERVIX: CERATINUS CYST(S)

NUMBER EXAMINED: 0

0 0 0 0 0 0

--ENDOMETRIUM: NEMATOCYST

NUMBER EXAMINED: 0

0 0 0 0 0 0

PITUITARY GLAND (PG)

NUMBER EXAMINED: 49

49 49 49 49 49 49

--B-PARS DISTALIS ADENOMA

NUMBER EXAMINED: 22

22 22 22 22 22 22

--NECROSIS/NEPHATOCYSTS

NUMBER EXAMINED: 15

15 15 15 15 15 15

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*** PATH/TOX SYSTEM OUTPUT ***
A TWENTY-FOUR MONTH FEEDING STUDY
IN RATS WITH DRG 3770
INCIDENCE SUMMARY

STUDY NUMBER: 852938

--- NUMBER OF ANIMALS AFFECTED ---

TABLE INCLUDES:

SEX=ALL; GROUP=ALL; SCREEN=ALL; WEEKS=ALL
DEATH=ALL; FIND=ALL; SUNSET=1

SEX: MALE FEMALE
GROUP: -1- -2- -3- -4- -1- -2- -3- -4-

NUMBER: 50 50 50 50 50 50 50 50 50 50

ORGAN AND FINDING DESCRIPTION

.. FROM PREVIOUS PAGE ..

	49	44	38	50	50	50	50	50	50	50	50	50	50	50	50
PITUITARY GLAND (PG)	9	4	4	2	1	1	1	1	1	1	1	1	1	1	1
--PARS DISTALIS: HYPERPLASIA	4	3	2	3	3	3	1	0	1	0	1	0	1	0	1
--PARS INTERMEDIA: CYSTS	1	2	3	2	3	2	3	2	7	3	3	2	7	3	3
--PARS DISTALIS: CYSTS	5	1	1	1	1	0	2	0	1	1	0	2	0	1	1
--CONGESTION	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0
--PARS NERVOSA: CYSTIC CHANGE	0	1	0	0	0	2	1	1	3	1	1	1	1	1	3
--PARS DISTALIS: CARCINOMA	0	0	0	0	0	0	0	0	1	0	1	0	1	0	1
--S-METASTATIC NEOPLASM	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0
--PARS DISTALIS: DYSTROPHIC MINERALIZATION	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0
--ACUTE INFLAMMATION/NECROSIS	0	0	0	0	0	0	0	0	1	0	0	0	0	0	1

	48	49	50	46	50	49	50	50	50
THYROID GLAND (TH)	7	5	4	4	7	7	6	5	5
--C-CELL HYPERPLASIA	5	3	7	2	2	2	3	3	3
--B-C-CELL ADENOMA	0	0	1	0	0	1	1	0	0
--N-C-CELL CARCINOMA	3	4	5	5	1	2	1	2	2
--FOLLICULAR CYST(S)	1	4	5	9	1	1	1	1	1
--B-FOLLICULAR CELL ADENOMA/CYSTADENOMA	0	1	1	3	0	0	1	0	1
--N-FOLLICULAR CELL CARCINOMA	8	8	8	5	7	5	6	7	7
--ULTRABRANCHIAL REST	1	0	1	1	0	0	0	0	0
--FOLLICULAR CELL HYPERPLASIA	0	0	0	1	0	0	0	0	0
--ABSCESS(ES)	0	0	0	0	0	0	0	0	0

	46	48	44	45	46	48	44	45
PARATHYROID GLS. (PT)	17	14	14	12	5	2	0	0
--HYPERTROPHY/HYPERPLASIA	0	0	0	2	0	0	0	1
--B-ADENOMA	0	0	0	0	0	0	0	0

	50	41	43	49	50	42	44	50
ADRENAL GLANDS (AD)	7	6	3	7	7	9	12	9
--U/CORTEX: CELL ALTERATION/DEGENERATION	1	2	6	1	1	3	0	5
--B/CORTEX: CELL ALTERATION/DEGENERATION	1	3	0	1	0	0	3	0
--U/CORTEX: VACUOLATION	4	4	1	4	0	1	2	0
--B/CORTEX: VACUOLATION	0	1	1	0	3	2	1	1
--B-U/CORTEX: ADENOMA	1	0	0	0	0	0	0	1
--N-U/CORTEX: CARCINOMA	1	0	0	0	0	0	0	1
--B-U/CORTEX: CARCINOMA	0	0	0	0	0	0	0	1
--U/NEPHROCYSTS	0	0	0	0	0	0	0	1
--B/NEPHROCYSTS	0	0	0	0	0	0	0	1
--U/MEDULLA: BASOPHILIC FOCI/AREAS	0	0	0	0	0	0	0	1
--B/MEDULLA: BASOPHILIC FOCI/AREAS	3	1	0	0	1	18	23	22
--U/CONGESTION	2	1	0	2	2	0	0	0
--B/CONGESTION	0	0	1	0	0	0	0	0

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*** PATH/TOX SYSTEM OUTPUT ***
 A TWENTY-FOUR MONTH FEEDING STUDY
 IN RATS WITH ORG 3770
 INCIDENCE SUMMARY

PRINTED: 10-MAY-90
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STUDY NUMBER: 252938

--- NUMBER OF ANIMALS AFFECTED ---

TABLE INCLUDES:

SEX=ALL; GROUP=ALL; SCREEN=ALL; WEEKS=ALL
 DEATH=ALL; FIND=ALL; SUBSET=1

SEX: -----MALE----- -----FEMALE-----
 GROUP: -1- -2- -3- -4- -1- -2- -3- -4-

ORGAN AND FINDING DESCRIPTION

NUMBER: 50 50 50 50 50 50 50 50

--- FROM PREVIOUS PAGE ---

ADRENAL GLANDS (AD)	NUMBER EXAMINED:	50	41	43	49	50	42	44	50
--S/CONGESTION		10	11	12	4	18	15	20	13
--S-U/PNEOCHROMOCYTOMA		3	3	1	2	1	1	0	2
--S-B/PNEOCHROMOCYTOMA		1	2	5	0	0	0	0	0
--U/CORTEX: NECROSIS		2	0	1	0	0	1	1	0
--B/CORTEX: NECROSIS		0	0	0	0	1	0	0	2
--U/DYSTROPHIC MINERALIZATION		1	1	0	0	0	0	0	1
--N-U/PNEOCHROMOCYTOMA		1	1	0	0	0	1	0	1
--N-B/PNEOCHROMOCYTOMA		0	0	1	0	0	0	0	0
--S-U/METASTATIC NEOPLASM		0	0	0	0	0	0	1	0
--S-B/METASTATIC NEOPLASM		0	1	0	0	0	1	0	0
--U/CORTEX: ATROPHY		0	0	2	0	0	0	0	1
--U/MEDULLA: ACUTE INFLAMMATION/NECROSIS		0	0	0	0	1	0	0	0
--B/EXTRAMEDULLARY HEMATOPOIESIS		0	0	0	0	0	1	0	0
--B/ACUTE INFLAMMATION		0	0	0	0	0	0	1	0

EYES (EY)	NUMBER EXAMINED:	48	38	39	48	49	33	37	50
--U/RETINAL ATROPHY		0	0	0	0	2	1	1	1
--B/RETINAL ATROPHY		0	0	0	0	0	0	0	1
--U/LENTICULAR FIBERS: DEGENERATION/SWELLING		0	2	1	0	1	0	2	0
--U/ACUTE KERATITIS		2	2	7	2	3	3	2	3
--B/ACUTE KERATITIS		2	2	1	1	1	1	0	0
--U/CHRONIC KERATITIS/NEOVASCULARIZATION		0	0	0	0	4	0	2	1
--B/CHRONIC KERATITIS/NEOVASCULARIZATION		1	0	0	0	0	0	0	0
--U/ACUTE ANTERIOR UVEITIS		0	0	3	0	1	0	0	1
--B/ACUTE ANTERIOR UVEITIS		1	1	0	0	1	2	0	0
--N-U/GLIOMA		0	1	0	0	0	0	0	0
--U/RETROBULBAR HEMORRHAGE		1	1	2	2	3	0	1	6
--U/PHTHISIS BULBI		1	1	0	0	0	0	6	1
--B/CORNEA: MINERALIZATION		0	0	0	0	1	0	0	0
--S-B/METASTATIC NEOPLASM		0	1	0	0	0	0	0	0
--B/IRIS: HEMORRHAGE		0	0	0	0	0	1	0	0

MUSC (BICEP FEM) (SM)	NUMBER EXAMINED:	50	36	37	50	50	29	34	50
--STEATOSIS		1	0	0	0	0	0	0	0
--S-METASTATIC NEOPLASM		1	0	0	0	0	0	0	0
--N-RHABDOMYOSARCOMA		0	0	0	1	0	0	0	0

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PRINTED: 10-MAY-90
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*** PATH/ION SYSTEM OUTPUT ***
A TWENTY-FOUR MONTH FEEDING STUDY
IN RATS WITH ORG 3770
INCIDENCE SUMMARY

STUDY NUMBER: 852938

--- NUMBER OF ANIMALS AFFECTED ---

TABLE INCLUDES:

SEX=ALL; GROUP=ALL; SCREEN=ALL; WEEKS=ALL
DEATH=ALL; FIND=ALL; SUBSET=1

SEX: ---MALE---FEMALE---
GROUP: 1- 2- 3- 4- 1- 2- 3- 4-

NUMBER: 50 50 50 50 50 50 50 50

ORGAN AND FINDING DESCRIPTION

SKIN (SK) NUMBER EXAMINED: 50 42 45 49 50 41 44 49

--HYPOTRICHOSSIS..... 10 6 6 2 9 10 10 9

--M-BASAL CELL CARCINOMA..... 1 0 0 0 0 0 0 0

--S-SQUAMOUS CELL PAPILLOMA..... 3 2 1 2 2 1 0 1

--M-SQUAMOUS CELL CARCINOMA..... 0 0 0 0 0 0 0 0

--EPIDERMOID CYST(S)..... 2 2 3 8 0 1 0 0

--ABSCESS(ES)..... 1 0 0 0 0 0 0 0

--KELOID..... 1 0 0 0 0 0 0 0

--ACUTE/SUBACUTE INFLAMMATION..... 3 3 1 3 4 2 7 3

--NECROSIS..... 2 3 1 1 4 1 3 3

--CHRONIC INFLAMMATION/FIBROSIS..... 0 1 0 2 0 0 0 0

--S-METASTATIC NEOPLASIA..... 0 1 0 0 0 0 0 0

--M-MYXOMA..... 1 0 0 0 0 0 0 0

--B-FIBROMA..... 0 2 0 1 0 0 0 0

--M-EMBRYONIC SARCOMA..... 0 0 0 0 0 0 0 0

--EPIDERMIS: HYPERPLASIA..... 0 0 0 0 1 0 0 0

--HYPERKERATOSIS..... 0 0 0 0 1 0 0 0

--B-BENIGN SQUAMOUS KERATOSIS/KERATOTIC PAPILLOMA..... 0 1 5 3 0 0 1 1

--M-ELIROSARCOMA..... 0 0 0 0 1 1 1 1

--B-MYXOMA..... 0 0 0 0 0 0 0 0

--SURFACE: FREE BLOOD..... 0 0 0 0 0 0 0 0

--B-HEMANGIOMA..... 0 0 0 0 0 0 0 0

--SURFACE: INFLAMMATORY CELLULAR DEBRIS..... 0 0 0 0 0 0 0 0

--M-SEBACEOUS CELL CARCINOMA..... 1 0 0 0 0 0 0 0

MAMMARY GLAND (MG)

..... NUMBER EXAMINED: 42 27 30 37 50 40 41 48

--GALACTOCYCLE..... 7 5 5 6 31 28 33 35

--B-FIBROADENOMA..... 0 0 0 0 1 2 2 1

--B-ADENOMA..... 0 0 0 0 0 0 0 0

--B-FIBROMA..... 0 0 0 0 0 0 0 0

--B-CARCINOMA..... 0 2 0 0 14 13 15 18

--BROWN PIGMENT..... 3 3 2 0 0 0 0 0

--PERIARTERITIS MOOOSA..... 1 0 0 0 1 0 0 0

--M-FIBROSARCOMA..... 1 0 0 0 1 0 0 0

--ACUTE INFLAMMATION/NECROSIS..... 0 1 0 0 1 0 0 0

--B-MYXOMA..... 0 1 0 0 1 0 0 0

--S-METASTATIC NEOPLASIA..... 0 2 0 0 0 0 0 0

--DUCTAL/ACIRAR HYPERPLASIA..... 0 0 0 0 2 0 0 0

--M-CARCINOSARCOMA..... 0 0 0 0 0 0 0 0

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*** PATH/TOX SYSTEM OUTPUT ***
A TWENTY-FOUR MONTH FEEDING STUDY
IN RATS WITH ORG 3770
INCIDENCE SUMMARY

STUDY NUMBER: 852938

--- NUMBER OF ANIMALS - AFFECTED ---

TABLE INCLUDES:

SEX=ALL; GROUP=ALL; SCREEN=ALL; WEEKS=ALL
DEATH=ALL; FIND=ALL; SUBSET=1

SEX: ---MALE---FEMALE---
GROUP: -1- -2- -3- -4- -1- -2- -3- -4-

NUMBER: 50 50 50 50 50 50 50 50

ORGAN AND FINDING DESCRIPTION

** FROM PREVIOUS PAGE **

MAMMARY GLAND (MG) NUMBER EXAMINED: 42 27 30 37 50 40 41 48

--NECROTOMA

--MEMORNAE

--B-LIPOMA

GENERAL COMMENTS (GC) NUMBER EXAMINED: 0 1 0 0 0 0 0 0

TAIL (TA) NUMBER EXAMINED: 23 23 24 22 8 8 3 5

--ACUTE INFLAMMATION/NECROSIS

--HYPERKERATOSIS

--SQUAMOUS CELL HYPERPLASIA

--ABSCESS(ES)

--B-SQUAMOUS CELL PAPILLOMA

--EPIDERMOID CYST(S)

--SURFACE INFLAMMATORY DEBRIS

--CHRONIC INFLAMMATION

--B-FIBROMA

URETERS (UR) NUMBER EXAMINED: 1 1 0 0 0 0 0 1

--U/LUMEN:DILATION

--U/LUMEN:DILATION

--U/LUMEN:UROLITHS

--U/ACUTE/SUBACUTE INFLAMMATION

EARS (EA) NUMBER EXAMINED: 15 8 12 16 13 14 15 12

--U/DISCONTINUITY

--U/CHONDROID HYPERPLASIA

--U/CHONDROID HYPERPLASIA

--U/ACUTE INFLAMMATION/NECROSIS

--U/CHRONIC INFLAMMATION/FIBROSIS

--U/SURFACE INFLAMMATORY DEBRIS

--U/CHRONIC ACTIVE INFLAMMATION

--U/CHRONIC ACTIVE INFLAMMATION

--U/EPIDERMOID CYST(S)

--U/HYPERKERATOSIS

--B-U/SQUAMOUS CELL PAPILLOMA

LYMPH NODE (LN) NUMBER EXAMINED: 21 17 12 20 11 6 8 11

--LYMPHOID CELL HYPERPLASIA

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*** PATH/TOX SYSTEM OUTPUT ***
A TWENTY-FOUR MONTH FEEDING STUDY
IN RATS WITH ORG 3770
INCIDENCE SUMMARY

PRINTED: 10-MAY-90
PAGE: 14

STUDY NUMBER: 852938

ORGANON Inc.

TABLE INCLUDES:

SEX=ALL; GROUP=ALL; SCREEN=ALL; WEEKS=ALL
DEATH=ALL; FIND=ALL; SUBSET=T

--- NUMBER OF ANIMALS AFFECTED ---

ORGAN AND FINDING DESCRIPTION	SEX: -----MALE-----				-----FEMALE-----			
	GROUP: -1-	-2-	-3-	-4-	-1-	-2-	-3-	-4-
NUMBER:	50	50	50	50	50	50	50	50
** FROM PREVIOUS PAGE **								
LYMPH NODE (LN) NUMBER EXAMINED:	21	17	12	20	11	6	8	11
--CONGESTION/HEMORRHAGE	10	7	6	5	4	2	2	1
--RETICULOENDOTHELIAL CELLS: BROWN PIGMENT	0	1	0	0	0	0	0	0
--SINUSOIDAL ECTASIA/CYSTS	5	4	6	10	2	0	0	2
--PLASMA CELL HYPERPLASIA	5	3	1	1	2	0	3	4
--LYMPHOID CELLS: NECROSIS	1	0	0	0	1	0	0	0
--S-METASTATIC NEOPLASM	0	1	0	1	1	0	0	2
--ACUTE INFLAMMATION	0	0	0	0	2	0	0	0
PREPUTIAL GLAND (PP) NUMBER EXAMINED:	2	2	0	1	0	0	1	0
--ABSCCESS(ES)	1	1	0	1	0	0	0	0
--DUCTS: ACCUMULATION OF SECRETORY MATERIAL	0	1	0	0	0	0	1	0
--CHRONIC ACTIVE INFLAMMATION	1	0	0	0	0	0	0	0
AORTA (AO) NUMBER EXAMINED:	6	2	5	3	3	1	0	0
--MINERALIZATION	3	1	2	1	3	1	0	0
--LUMEN: DILATION	3	0	4	2	0	1	0	0
--M-AORTIC BODY, CHEMOECTOMA	0	1	0	0	0	0	0	0
EXTREMITIES (EX) NUMBER EXAMINED:	15	17	16	9	5	6	4	2
--ACUTE INFLAMMATION/NECROSIS	12	13	7	4	3	4	2	0
--CHRONIC ACTIVE INFLAMMATION	2	2	8	3	1	0	2	1
--EPIDERMOID CYST(S)	0	0	0	1	0	1	0	0
--SUBCUTANEOUS EDEMA	0	0	0	0	0	0	0	1
--CHRONIC INFLAMMATION/FIBROSIS	0	1	1	0	0	0	0	0
MESENTERY/PERIT (MS) NUMBER EXAMINED:	4	3	1	1	2	3	3	2
--FAT NECROSIS	1	1	0	0	0	3	0	0
--S-METASTATIC NEOPLASM	1	0	0	0	0	0	2	0
--MESENTERIC ARTERIES: MINERALIZATION	1	0	0	0	0	0	0	0
--MESENTERIC ARTERIES: THROMBUS	1	1	0	0	0	0	0	0
--MESENTERIC ARTERIES: PERIARTERITIS NODOSA	1	2	1	0	1	0	0	0
--M-PERITONEUM: MALIGNANT MESOTHELIOMA	0	0	0	0	0	0	0	1
--HEMORRHAGE	0	0	0	1	0	0	0	0
--B-HYXOMA	0	0	0	0	0	0	1	0
VAGINA (VA) NUMBER EXAMINED:	0	0	0	0	4	9	7	3
--LUMEN: ACCUMULATION OF INFLAMMATORY CELLS/CELL DEBRIS	0	0	0	0	3	7	5	3
--LUMEN: DILATION	0	0	0	0	0	0	1	0

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*** PATH/TOX SYSTEM OUTPUT ***
 A TWENTY-FOUR MONTH FEEDING STUDY
 IN RATS WITH ORG 3770
 INCIDENCE SUMMARY

PRINTED: 10-MAY-90
 PAGE: 15

STUDY NUMBER: 052930

TABLE INCLUDES:

SEX=ALL; GROUP=ALL; SCREEN=ALL; WEEKS=ALL
 DEATH=ALL; FIND=ALL; SUBSET=T

--- NUMBER OF ANIMALS AFFECTED ---

ORGAN AND FINDING DESCRIPTION	NUMBER	SEX: -----MALE-----				-----FEMALE-----			
		GROUP: -1-	-2-	-3-	-4-	-1-	-2-	-3-	-4-
		50	50	50	50	50	50	50	50
BULBOURETHRAL GD (BU) --HEMORRHAGE	NUMBER EXAMINED:	0	0	1	0	0	0	0	0
		0	0	1	0	0	0	0	0
LACRIMAL GLANDS (LG) --ECTOPIC HARDERIAN GLAND	NUMBER EXAMINED:	1	0	1	0	0	0	0	0
		1	0	1	0	0	0	0	0
ADIPOSE TISSUE (AT) --SUBCUTANEOUS EDEMA --FAT NECROSIS	NUMBER EXAMINED:	0	1	1	0	0	1	0	0
		0	0	1	0	0	0	0	0
		0	1	0	0	0	1	0	0
PENIS (PE) --ACUTE INFLAMMATION/NECROSIS --CONGESTION	NUMBER EXAMINED:	0	1	1	0	0	0	0	0
		0	1	0	0	0	0	0	0
		0	0	1	0	0	0	0	0
HARDERIAN GLANDS (HG) --S-B/METASTATIC NEOPLASM	NUMBER EXAMINED:	0	1	0	0	1	0	0	0
		0	1	0	0	0	0	0	0
TONGUE (TO) --HEMATOMA	NUMBER EXAMINED:	0	1	0	0	0	0	0	0
		0	1	0	0	0	0	0	0
LYMPHO/RET.NEOPH (LR) --H-HISTIOCYTIC SARCOMA --H-MALIGNANT LYMPHOMA/LYMPHOCYTIC LEUKEMIA --H-GRANULOCYTIC LEUKEMIA/MYELOSARCOMA --H-MONONUCLEAR CELL LEUKEMIA	NUMBER EXAMINED:	3	3	0	2	2	1	2	0
		2	2	0	0	0	0	2	0
		1	0	0	1	2	6	0	0
		0	1	0	1	0	0	0	0
		0	0	0	0	0	1	0	0

** END OF LIST **

ORGANON Inc.

0469

REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA

NDA 20-415

Reviewer:

Steven Sparenborg, Ph.D.

Dates:

Written Review - September 20, 1995

Filing Date - March 30, 1995

User Fee Due Date - January 30, 1996

Sponsor:

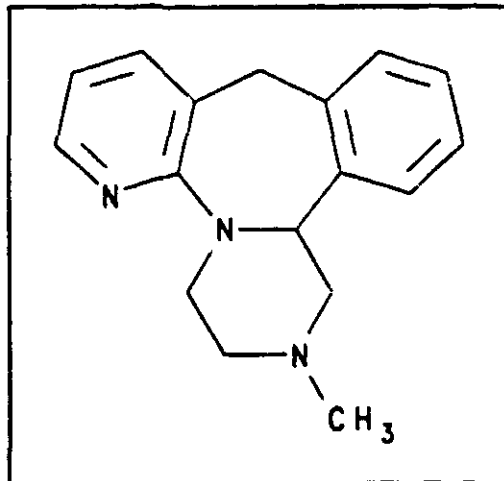
Organon, Inc.
West Orange, NJ

Drug:

REMERON® (6-azamianserin, mirtazapine, ORG 3770)

Chemical name:

1, 2, 3, 4, 10, 14b-hexahydro-2-methylpyrazino [2, 1-2] pyrido
[2,3-c][2]benzazepine



Category:

α_2 , 5-HT₂, 5-HT₃ antagonist

Indication:

depression

Related IND's:

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GLP

All toxicity studies were conducted in accordance w/FDA GLP, except as noted within individual study reviews.

Note: Portions of this review excerpted from the sponsors submission are enclosed within quotation marks.

Pharmacokinetics

1. Pharmacokinetics of ORG 3770 after a single oral administration to rats and dogs

Six male WU rats were given a 20 mg/kg dose of Org 3770 and 2 male and 2 female beagle dogs were given 5 mg/kg. The parent drug was measured with GC. The drug is rapidly absorbed in rats.

Rats

t_{max} (min)	22 ± 13
C_{max} (ng.ml)	903 ± 238
AUC_{0-24h} (µg.min/ml)	97 ± 68

Dogs

t_{max} (min)	60-90
C_{max} (ng.ml)	142-204
AUC_{0-26h} (µg.min/ml)	16-34

A. Pharmacokinetics of Org 3770 after single i.v. administration to rats and dogs

The plasma kinetics of Org 3770 (1-2 mg/kg i.v.) were studied in male and female beagle dogs and WU and DA rats (the latter strain is considered to be a "slow oxidator"). Pharmacokinetic parameters are summarized in table 1. After an initial redistribution phase, the plasma half-life of Org 3770 was 2-4 hr in both species. The DA rat had the longest half-life and the slowest clearance, as expected. Female WU rats eliminated Org 3770 slightly more slowly than males. There was no evidence of nonlinearity. In a separate study in Wistar rats, nephrectomy resulted in only a modest increase in the half life (70%) and decrease in the clearance (-45%) of Org 3770.

Table I - Pharmacokinetic Parameters

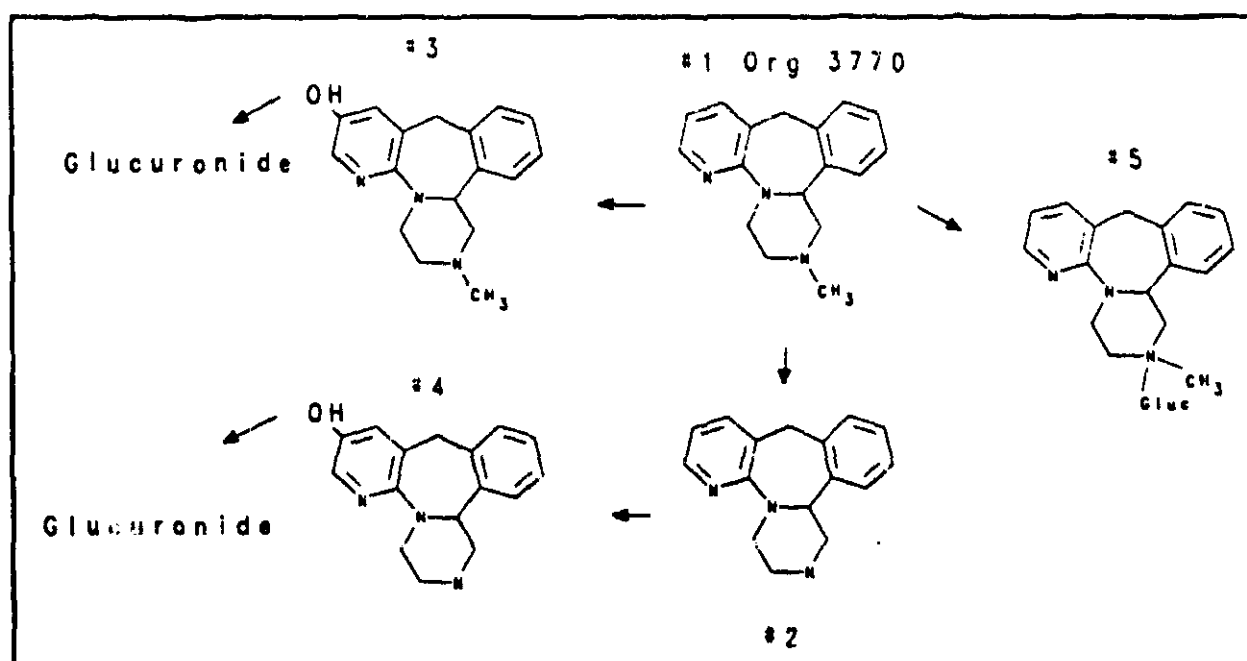
		Dog	WU ♂	WU ♀	DA ♀
$t_{1/2\alpha}$	(hr)	0.4	0.2	0.4	0.6
$t_{1/2\beta}$	"	3.0	1.7	2.0	4.0
Vd	l/kg	20.	4.9	3.9	3.6
Cl	l/hr	25.	1.6	0.7	0.3

B. Biotransformation of Org 3770 in man and laboratory animals

The metabolic profile of Org 3770 was studied in humans, dogs, rabbits, guinea pigs, rats and mice. In the urine, metabolites glucuronidated at the 8 position (figure 1 - metabolites 3 and 4) were most prevalent, comprising 15-50% of the administered dose in all species.

Humans also had significant amounts (5-20%)

of metabolite 5 and its conjugates. Many of the same metabolites were found in the feces, but the amounts were not quantitated. The conjugate of metabolite #5 is thought to be a possible substrate for enterohepatic recirculation in humans and guinea pigs, which may explain a second, delayed peak in plasma plus metabolite levels in these species. Plasma

**Figure 1 - Metabolites of Org 3770**

constituents were mostly the parent compound and metabolites 2-4, but only the parent compound and the N-desmethyl metabolite (#2) were found in brain. Species-specific metabolites (not shown in figure 1) included the 8-hydroxy (N2) oxide (dog, rabbit), and the 13-hydroxy and carbamate glucuronides (mouse).

C. Excretion, accumulation and retention of radioactivity in male and female rats receiving oral doses of ^3H -Org 3770

A total of 48 Fawn Hooded rats were dosed with [$^{12}\text{-}^3\text{H}$]-Org 3770 (5 mg i.g. x 1-21 days) following which, plasma, feces, urine and tissue levels of radioactivity were monitored. Urinary excretion of radioactivity accounted for 27-38% of the Org 3770 dose administered after both single and multidose administration. Urinary excretion was more than 85% complete within 24 hr of dosing. Fecal excretion accounted for 50-60% of the radioactivity administered. Excretion by this route was 80% or more complete within 24 hr of single or multiple Org 3770 doses. Tissue levels were highest in intestine (plus contents) and liver, followed by kidneys and stomach. Very low but measurable levels were found in the brain. Evidence of accumulation (up to 100% increase in tissue:plasma ratio after multiple vs. single dosing) was found in brain, eyes, skin, heart and lung. Low levels of radioactivity were retained in the skin for 1 week or more after dosing was discontinued.

D. Binding of Org 3770 to human plasma proteins and human liver proteins

The binding of ^3H -Org 3770 (0.01-10 $\mu\text{g/ml}$) to human plasma and liver proteins was determined by equilibrium dialysis. The bound fraction of Org 3770 in human plasma was approximately 85% over the concentration range tested. Binding was reversible and nonspecific. In the presence of human liver proteins, tissue binding of Org 3770 was 3-fold higher than plasma binding. Saturation did not occur at Org 3770 concentrations of up to 10 $\mu\text{g/ml}$.

E. "Placental Transfer and excretion of radioactivity via the milk in rats after a single oral dose of [^3H]-Org 3770"

Two pregnant SD rats received a dose of 6.2 mg of labeled drug on Day 18 of gestation. Plasma and blood levels of the radioactivity were measured 2 hrs later from the mother and from the ground-up fetuses. Two lactating rats received a dose of 5.4 mg 15 days after parturition. Radioactivity in the mothers blood and the stomach contents and total body of the pups was measured 5 hrs later. 0.03% of the maternal dose was found in the average fetus and 0.38% of the maternal dose was found in single pups. Most of the metabolites found in the mother were also found in the fetuses and pups.

Chronic Toxicity

NATURE OF SUBMISSION: A CHRONIC TOXICITY STUDY IN RATS WITH ORG 3770

ANIMAL: Sprague-Dawley Rat

DOSE: 0, 2.5, 20, and 120 mg/kg/day in diet

DURATION: 52 weeks

FINDINGS:

This study, conducted for Organon International, was designed to assess the potential chronic toxicity of Org 3770 when administered orally, via dietary admixture to 200 Sprague-Dawley CD rats. Thirty animals per sex were administered the test substance at dose levels of 2.0 mg/kg/day (Group II), and 20.0 mg/kg/day (Group III), and 40/sex at a dose level of 120.0 mg/kg/day (Group IV), for a period of twelve months. Following the treatment period, up to 10 animals/sex/group in Groups I and IV were placed on a thirty-four day untreated recovery period. Control animals (40/sex) received standard laboratory diet.

Physical observations, ophthalmoscopic examinations, body weight and food consumption measurements were performed on all animals pretest and at selected intervals during the treatment period. Hematology, clinical chemistry, and urinalysis were performed on selected animals pretest and at selected intervals during the treatment period.

After six months of treatment, an interim sacrifice was performed on up to ten animals/sex/group. Following twelve months of treatment up to twenty animals/sex/group were sacrificed. The remaining animals in the control and high-dose groups remained on test for a 34-day untreated recovery period. Complete gross postmortem examinations were performed on all animals placed on test. Selected organs were weighed and organ/body weight ratios calculated at the scheduled sacrifice intervals. Histopathological evaluation of selected tissues was performed on all animals dying spontaneously or killed accidentally, as well as all control and high-dose animals killed at the month 6 and terminal sacrifice intervals. Kidney samples from one animal/sex/group from the control and high-dose groups from the terminal sacrifice were examined via electron microscopy. In addition, the kidneys of the low- and mid-dose animals killed at the month 6 and terminal sacrifice, as well as all recovery animals were examined microscopically. An additional set of kidney slides were prepared for 3 animals/sex/group randomly selected from the animals sacrificed at the month 6 interval, and stained with Oil Red-O and PAS and examined microscopically. Kidney sections from a total of 6 animals (3 control and 3 high-dose) were stained with Iron Reaction, Lipofuscin, Bile and Calcium from the month 6 interim sacrifice. Kidney slides were also prepared at the terminal sacrifice from 4 animals from the high-dose group and 3 animals from the control group and stained for Acid-fast Lipofuscin using the Ziehl Neelsen method and examined microscopically.

Results:

From the parameters evaluated in this study only those findings which were considered to be treatment-related effects are presented below. Body weights of the low-dose males and low- and mid-dose females were generally slightly lower than the control animals during the course of the study. However, body weight gain of these groups parallel that of the control animals from Weeks 12 through 49. Therefore, this change was considered to be an early transitory effect which did not progress or worsen over time. A marked and progressive body weight effect was evident in the high-dose animals which progressed from a body weight decrement of approximately 6-7 percent at week 1 to 28 and 33 percent in the males and females respectively at week 49.

Food consumption of the high-dose females was generally greater than the control animals from weeks 1 through 49 of the study.

The results of gross, light microscopic and electron microscopic examinations demonstrated a mild reversible effect on the kidneys of high-dose males and to a lesser degree in female rats. The renal change was characterized by cytoplasmic vacuolation of the tubular epithelium, not accompanied by cellular degeneration or necrosis, resulting from an increase in the size and number of vacuoles constituting the endocytotic/lysosomal system and by the presence of brown pigment in the tubular cytoplasm. These changes were partially reversible, following a one month recovery period.

All other parameters evaluated: physical observations; ophthalmoscopic examinations; hematology and clinical chemistry studies; urinalysis data, gross anatomy and terminal organ and organ/body weight ratio data, did not reveal any indications of adverse, treatment-related effects.

(This review signed by R. Hollenbeck)

A 52 week oral toxicity study with a 6 month interim sacrifice with Org 3770 in beagle dogs (conducted by Organon, Oss, The Netherlands)

A total of 56 beagle dogs were subdivided into the following groups:

<u>Group</u>	<u># of Animals</u>		<u>Dose (mg/kg)</u>
	<u>M</u>	<u>F</u>	
C	8	8	Control
LD	6	6	2.5
MD	6	6	15
HD	8	8	80

Org 3770 (batch N) tablets were administered orally for 1 year. 3 animals/sex-group were sacrificed after 6 months of dosing. 3 animals/sex-group were sacrificed after 12 months, and 2 animals/sex in the C and HD groups were allowed to recover for 5 weeks before sacrifice.

Observations:

Daily	Mortality and general condition
	Food consumption
Weekly	Body weight
Weeks 0, 6, 12, 25, 39 & 51	Physical examination
	Hematology
	Clinical chemistry
	Urinalysis
Weeks 0, 25 & 51	Ophthalmological examination
	Neurological examination
	Glucose tolerance test
Termination	Necropsy
	Organ weights
	Histopathology
	Myelograms

Results:

1. There was no premature mortality during this study.
2. Behavioral signs of toxicity included decreased food consumption and diarrhea (observed in all groups but with higher frequency in HD animals), as well as emesis and tremor (HD group only). A single HDM exhibited preconvulsive signs during physical examination and later experienced tonic/clonic convulsions 4-5 hr after dosing.
3. HD animals had decreases in body weight gain throughout the study. During the first 4 weeks, HDM gained 4-5% less weight while HDF gained 1-2% less than controls. By 6 months, the deficits in weight gain were 13-17%, whereas at 12 months body weight gains were 7-20% less than controls. Recovery was incomplete 4 weeks later. Weight gain was unaffected in the other Org 3770 groups.
4. Food consumption was generally comparable in all groups, with only occasional slight decreases in consumption in the HD group.

5. Ophthalmologic examination indicated a lack of pupillary dilation after administration of mydriatic agent in HD animals at week 25 and increased incidence of red conjunctiva in HD animals at week 51. Results of neurological examinations were inconclusive.
6. Pulse rates appeared to be increased in the HDM group compared to controls. Although differences were not statistically significant, at all time points except week 0, week 39 and week 56 (recovery), the HDM group means were 2-20% higher than the highest C group mean recorded at any time point.
7. HD animals displayed consistent decreases in HBG (7-20%), PCV (5-14%) and RBC counts (2-15%) beginning at week 6. Recovery values were generally normal. MD animals also experienced a similar decrease in HBG at week 51 only. ESR was highly variable but appeared to be increased as much as 10-fold in HD animals compared to controls. Myelograms at autopsy revealed an increase of up to 80% in the erythroid/myeloid element ratio in MD and HD groups.

AlkP activity was increased throughout the dosing period in HDM (50-221%) and HDF (32-100%), and also to a lesser extent in MDF animals beginning at week 39. SGPT activities were elevated by 71-390% in MDM and HD animals, also beginning at week 39. Recovery values for both enzyme activities were normal. BUN was elevated by 18-36% throughout dosing in MD and HD animals, but the change was greater in the MD group. Serum potassium levels were elevated slightly (2-11%) in HD animals from weeks 12-51, but the sponsor reported that these values remained within the range of historical controls. LDH values were highly variable but appeared to be decreased in HD groups.

Urinalysis parameters were unremarkable.

8. Absolute and relative liver weights were increased by 3-39% at months 6 and 12 in all Org 3770 groups. The changes were greatest in the HD group, but disappeared during the recovery period. Absolute and relative adrenal weights were also increased by 20-47% and 31-69%, respectively, at these time points, but only in the HD group. HDF ovarian weights were increased by up to 83% at months 6 and 12. Absolute and relative spleen weights were decreased by 12-64% in all Org 3770 groups at the 6 month necropsy only.
9. Gross findings included hepatic enlargement (observed in all HD animals at 12 months, but not at recovery or 6 month interim sacrifice) and small thymus (all HDM at 12 months). Significant histopathologic findings from combined 6 and 12 month sacrifice groups are summarized in table 2. There was 1 neoplastic finding: a HDF with a granulosa cell tumor at month 6. This finding was considered to be spontaneous. Hepatic cell hypertrophy was observed in all HD animals at 12 months. It was not accompanied by any histopathologic indication of hepatic damage. Renal pyelitis was also noted in the HD group at 12 months. Pubertal thymic involution may have been accelerated in the HD group, but the incidence of this finding was high in all groups. Similarly, the variable state of sexual maturity in males may have contributed to scattered incidences of inhibited spermatogenesis. The sponsor's histopathology summary table is included as an appendix to this review.

Table II - Histopathology Summary

Tissue	C	LD	MD	HD
Liver:				
Hypertrophy	0	0	0	7
Focal necrosis	2	3	2	1
Kidney:				
Leukohistiocytic pyelitis	0	0	0	5
Monocyte infiltration	4	2	7	5
Ovary:				
Granulosa cell tumor	0	0	0	1
Testes:				
Inhibition of spermat- or spermiogenesis	1	1	0	3
Lung:				
Subpleural fibrosis	1	2	3	3
Pachypleura	6	9	4	6
Heart:				
Hematocyst and/or myodegeneration	1	2	2	0
Lymph nodes:				
Histiocytosis	3	3	2	4
Thymus:				
Pubertal involution	8	9	5	11

Carcinogenicity Studies

An 18 month carcinogenicity feeding study in mice with ORG 3770 (conducted by Bio/dynamics Inc., East Millstone, NJ)

A total of 400 CD-1 mice were subdivided into the following groups:

Group	# of Animals		Dose (mg/kg/day)
	M	F	
C	50	50	Vehicle
LD	50	50	2.0
MD	50	50	20.0
HD	50	50	200.0

ORG 3770 was administered in the diet for 18 months followed by sacrifice and necropsy.

Observations:

Daily	Mortality and general behavior
Weekly	Physical examination
	Body weights
	Food consumption
Months 12 & 18	Blood smears (C & HD only)
Termination	Necropsy
	Organ weights
	Histopathology (C, HD and early decedents)
	Liver electron microscopy (12 HDM only)

Results:

1. Rates and causes of premature mortality are summarized in figure 1 and table 1, respectively. Eighteen month survival was at least 50% in all groups, and was not affected by treatment with ORG 3770. The most common cause of early death was chronic nephropathy, not an unusual finding in aged mice. The number of deaths due to hepatocellular carcinoma was increased from 2 in CM to 5 in HDM. There were no other changes in cause of death.
- 1a. The FDA statistician, Dr. Daphne Lin, used the Cox test and the generalized Wilcoxon test to analyze survival. There were no significant effects. The data were analyzed by gender and by two time periods, 0-50 weeks and 51-78 weeks. The figure below uses 3 six-month time periods.

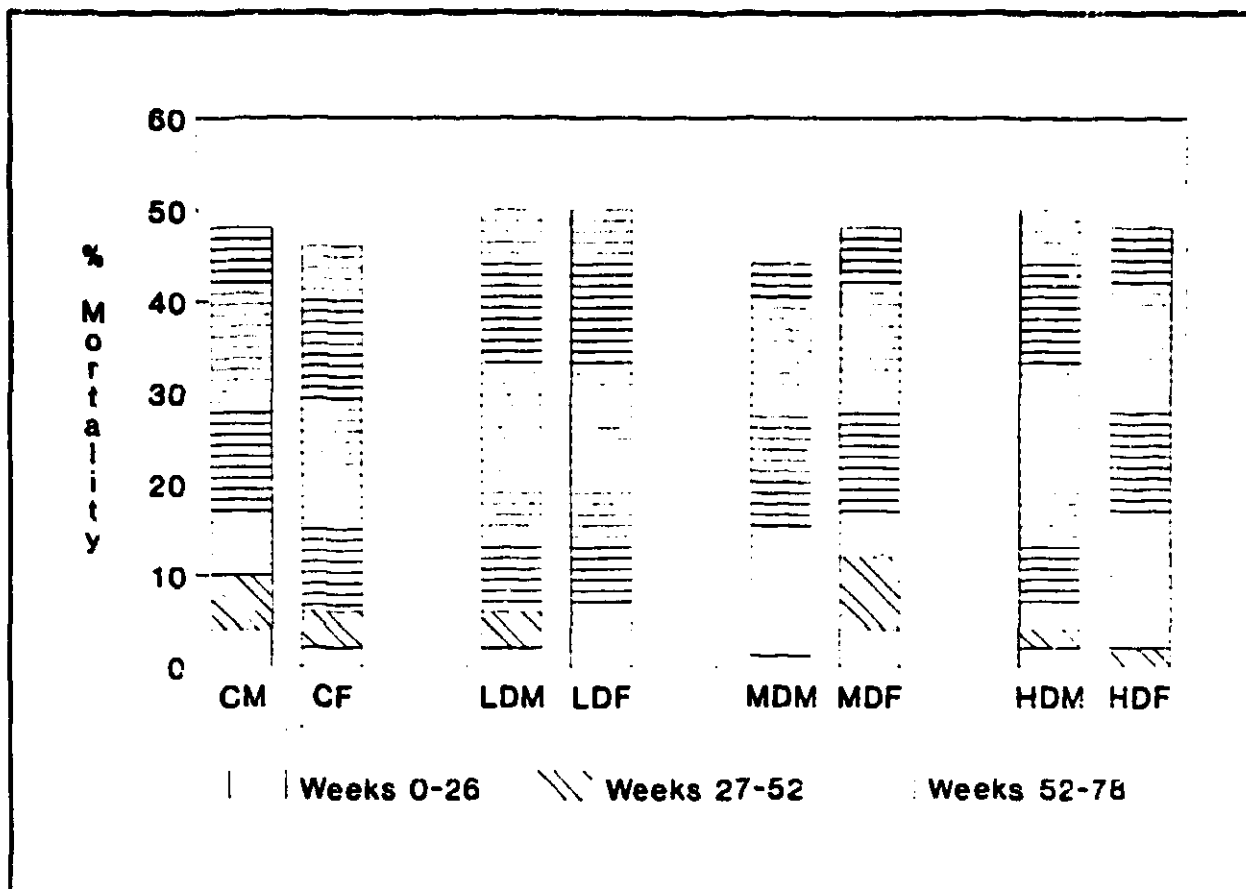
**Figure 3 - Premature Mortality**

Table III - Causes of Death

		C	LD	MD	HD
Chronic nephropathy	♂	7	14	13	9
	♀	11	17	15	19
Hepatocellular carcinoma	♂	2	1	2	5
Malignant lymphoma	♂	1	0	1	1
	♀	1	1	2	0
Hemangiosarcoma	♂	0	1	0	0
	♀	1	0	0	0
Histiocytic sarcoma	♂	0	0	0	1
	♀	1	0	1	0
Cardiac septic thrombosis	♂	1	0	1	1
	♀	1	0	0	0
Other neoplastic ^a	♀	1	1	1	1
Other nonneoplastic	♂	4	1	3	2
	♀	0	2	0	2
Unknown	♂	9	8	2	6
	♀	7	4	5	2

^aIncludes one case each of hepatocellular adenoma, mammary carcinoma, endometrial sarcoma and Granulocytic leukemia

2. There were no behavioral indications of drug-related toxicity. A number of observations were common in all groups, especially late in the study, including excess lacrimation and chronic dacryorrhea, yellow staining of the ano-genital region, alopecia and lens opacities. The number of animals with palpable tissue masses was not affected by ORG 3770 treatment.

3. HDM body weights were decreased relative to CM by up to 4-6% at sporadic time points and at the end of the study (figure 2). Body weights in all other groups were unaffected. Food consumption was increased sporadically by up to 15% in MDM and HD animals. Drug intake was maintained within $\pm 20\%$ of targeted levels.
4. Differential WBC counts were similar in C and HD animals.
5. Gross necropsy indicated an increase in drug-treated males with liver masses or nodules (10, 10, 22 and 28% in C, LD, MD and HD, respectively). This finding was confirmed histopathologically by an increased incidence of hepatic adenoma and carcinoma in HDM (table 2). The sponsor attributes this finding to induction of hepatic microsomal enzyme activity, and cites a previous study in which ORG 3770 induced activities of cytochrome P₄₅₀, aminopyrine-N-demethylase, aniline hydroxylase and several other hepatic enzymes. Comparison of electron photomicrographs of livers from 3 CM and 15 HDM revealed modestly increased smooth endoplasmic reticulum in the drug-treated animals, which is indicative of enzyme induction.

Examination of animals not bearing hepatic tumors did indicate an increase in hepatic vacuolation (10, 12, 17 and 13/50 in CM, LDM, MDM and HDM), possibly due to induction. However, the FDA statistical reviewer used the methods of Peto and the exact permutation trend test to analyze the tumor data. After correcting for multiple testing, no tumor types were found to be statistically significant except hepatocellular adenoma/carcinoma combined, in males only ($p = 0.0015$, linear trend; $p < .05$, control vs. HD paired comparison).

The most frequent nonneoplastic findings included amyloidosis of the heart, spleen, adrenals, liver and GI tract, chronic pneumonia, mesenteric congestion and lymphoid hyperplasia, chronic nephropathy, testicular degeneration and uterine endometrial hyperplasia. None of these appeared to be affected by ORG 3770 treatment, but instead were consistent with age-related findings in this species.

Table IV - Neoplastic Findings

	C	LD	MD	HD	
Hepatic adenoma	♂	3	3	6	10 ^a
	♀	1	2	1	0
Hepatic carcinoma	♂	4	2	5	8
	♀	0	0	0	1
Hepatic hemangioma/sarcoma	♂	1	3	1	0
	♀	3	2	1	0
Lung carcinoma/adenoma	♂	4	3	1	2
	♀	3	0	0	4
Malignant lymphoma	♂	1	0	1	1
	♀	3	1	2	2
Granulocytic leukemia	♀	0	0	0	1
Histiocytic sarcoma	♂	0	0	0	1
	♀	1	0	1	0
Testicular interstitial cell tumor	♂	0	1	1	0
Mammary carcinoma	♀	0	0	1	0
Ovarian cystadenoma	♀	0	1	1	0
Uterine sarcoma/leiomyoma	♀	2	1	1	1
Endometrial stromal polyps	♀	1	0	2	3
Other	♂	1	1	3	0
	♀	1	2	0	2
^a p < .05 vs. control (Fisher)					

B. A 24 month feeding study in rats with ORG 3770 (conducted by Bio/dynamics Inc., E. Millstone,NJ)

A total of 400 Sprague-Dawley CD rats were subdivided into the following groups:

<u>Group</u>	<u># of Animals</u>		<u>Dose (mg/kg/day)</u>
	<u>M</u>	<u>F</u>	
C	50	50	Vehicle
LD	50	50	2
MD	50	50	20
HD	50	50	60

ORG 3770 (batch P) was administered in the diet for 24 months followed by sacrifice and necropsy.

Observations:

Daily	Mortality and general behavior
Weekly	Physical examination
	Body weights
	Food consumption
Months 12, 18 & 24	Blood smears (C & HD only)
Termination	Necropsy
	Organ weights
	Histopathology (C, HD and early decedents)

Results:

1. Rates of premature mortality are summarized in figure 3. Overall 18 month survival ranged from 74-92% but 24 month survival was considerably lower (30-56%). Early deaths were increased in MDF (70% vs. 52% in CF, $p < .05$) but were decreased in HDM (44% vs. 70% in CM, $p < .01$). Individual causes of deaths were not provided for premature decedents.
2. The sponsor reported no behavioral observations indicative of drug-related toxicity. A number of findings including chromo dacryorrhea, excessive lacrimation and sores of the skin, tail and ears were observed in all groups, including controls.
3. Body weights were reduced by 8-39% in all drug treatment groups in a dose-related manner (figure 4).
4. Food consumption was comparable in all groups except for HDF, in which there were 5-30% increases. Drug consumption was generally maintained within 10% of target doses (range -20 to +57%). However, analysis of ORG 3770 content in the diet revealed fairly large variations (up to 50%) in the distribution of drug in the diet material.
5. Total and differential WBC data from C and HD animals were unremarkable.
6. Tumor data are summarized in table 3. ORG 3770 treatment was associated with an increase in thyroid follicular adenomas in all treated male groups and an increase in liver adenomas in the MDF and HDF groups. The increase in thyroid tumors was dose-related and appeared to be accompanied by an increase in thyroid follicular carcinomas in HDM. C-cell tumor frequencies were not significantly increased. The sponsor suggests that changes in thyroid follicular tumor frequency may have been secondary to induction of hepatic P450, but does not provide supporting evidence such as measurement of hepatic enzyme or

serum TSH levels. The increase in liver adenomas was evident only in females (MDF $p=0.058$ and HDF $p=0.028$ vs CF), and was not accompanied by changes in the frequency of other hepatic tumors (e.g. carcinoma). Although not statistically significant, there also appeared to be a general trend toward increased uterine neoplasms in the HDF group. Thus, there were increases in the frequency of uterine endometrial sarcomas (2 vs. 0), other uterine tumors (2 vs. 1) and uterine endometrial polyps (4 vs. 1), as well as cervical hyperplasia (2 vs. 0) in HDF vs. CF. The incidence of other neoplastic and nonneoplastic findings did not appear to be affected by ORG 3770. Total tumor counts and percentages of tumor bearing animals were also unaffected.

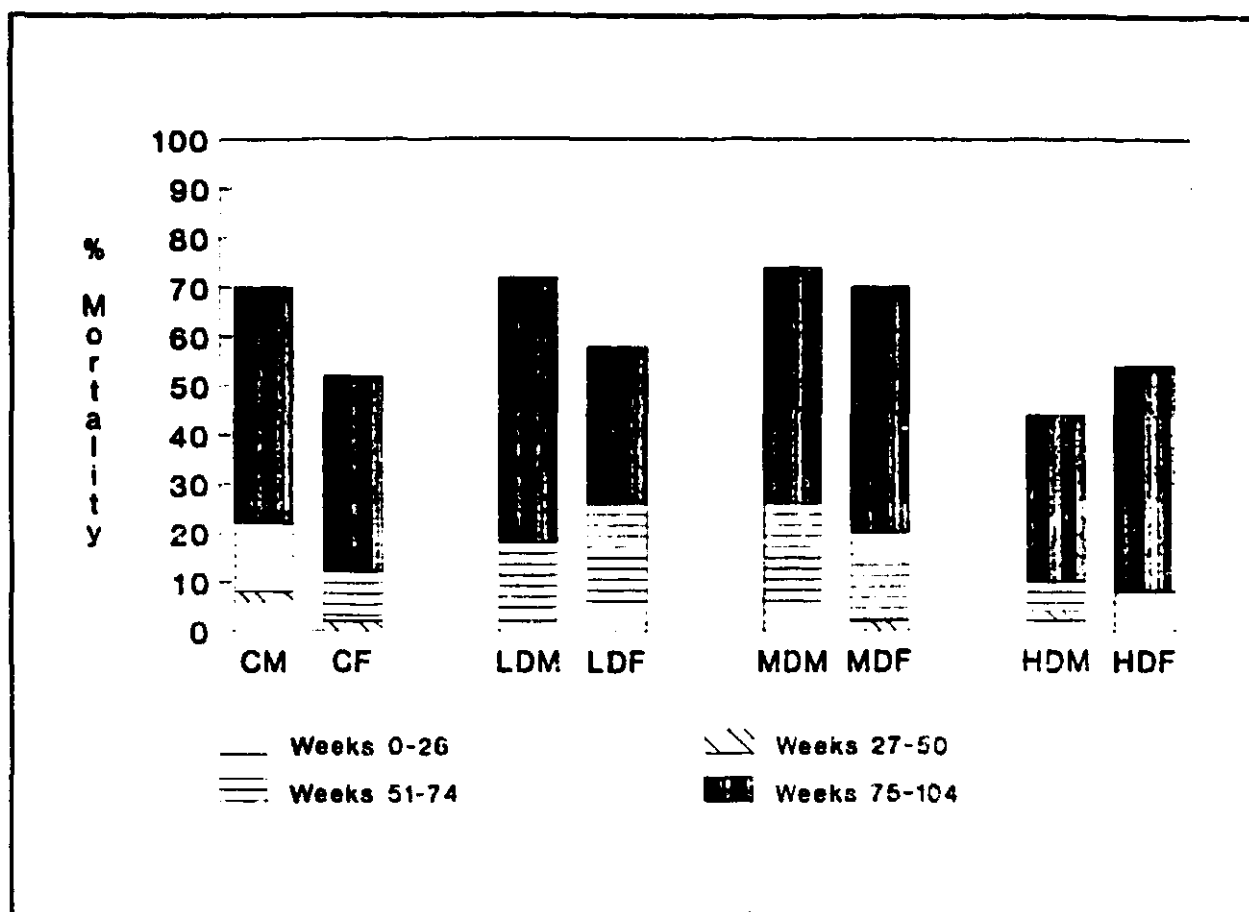


Figure 4 - Premature Mortality

Table 3 - Neoplastic Findings

		<u>C</u>	<u>LD</u>	<u>MD</u>	<u>HD</u>
Hepatocellular adenoma	♂	0	0	0	3
	♀	0	0	4	5 ^a
Hepatocellular carcinoma	♂	1	1	1	3
	♀	1	0	0	1
Thyroid follicular adenoma	♂	1	4	5	9 ^a
	♀	1	1	1	1
Thyroid follicular carcinoma	♂	0	1	1	3
	♀	0	0	1	0
Thyroid C-cell adenoma	♂	5	3	7	7
	♀	2	7	2	3
Thyroid C-cell carcinoma	♂	0	0	1	0
	♀	0	1	1	0
Testicular interstitial cell tumor	♂	0	2	0	3
Uterine endometrial sarcoma	♀	0	0	0	2
Other uterine/ovarian tumors	♀	1	0	0	2
Uterine endometrial polyps	♀	1	0	3	4
Mammary fibroadenoma	♀	12	11	13	7
Mammary adenoma	♀	1	2	2	1
Mammary fibroma	♀	4	0	0	0
Mammary carcinoma	♂	0	2	0	0
	♀	14	13	13	19
Mammary fibrosarcoma	♂	1	0	0	1
	♀	1	0	1	0
Mammary lipoma	♂	0	0	0	0
	♀	1	0	1	0
Adrenal adenoma	♂	0	1	1	0
	♀	3	2	1	3
Adrenal carcinoma	♂	1	0	0	0
	♀	0	0	0	2

Table 3 (continued)

Pheochromocytoma	♂	4	6	7	2
	♀	1	2	0	3
Pancreatic islet cell adenoma	♂	4	1	2	2
	♀	2	1	3	1
Pituitary adenoma	♂	22	24	22	22
	♀	41	43	45	35
Pituitary carcinoma	♂	0	1	0	0
	♀	2	1	1	3
Renal lipoma	♂	0	1	1	0
	♀	0	0	0	1
Brain glioma	♂	0	2	0	2
	♀	0	0	0	1
Skin squamous cell papilloma	♂	4	3	3	2
	♀	2	1	0	1
Skin squamous cell carcinoma	♂	0	0	0	1
	♀	0	0	0	1
Skin fibroma/fibrosarcoma	♂	0	2	0	2
	♀	1	1	4	2
Histiocytic sarcoma	♂	2	2	0	0
	♀	0	0	2	0
Malignant lymphoma	♂	1	0	0	1
	♀	2	0	0	0
Granulocytic leukemia	♂	0	1	0	1
	♀	0	0	0	0
Other	♂	3	3	1	5
	♀	2	2	1	2
# Tumor-bearing animals	♂	34	39	36	37
	♀	47	47	48	48
Total tumor count	♂	70	93	52	87
	♀	104	96	115	113

*p<.05 (Fisher)

The sponsor reported, as found in the above table, that there was a significant linear trend in hepatocellular adenoma in female rats. They discounted the statistical significance of this finding because the rate was within the range of their historical controls, but did not offer any data regarding this. In an independent collection of 585 Crl:CD rats tested between 1984 and 1991, the average rate of hepatocellular adenoma was 5% for males and females (McMartin, et al., *Toxicologic Pathology*, 1992, 20(2), 212-225). Another independent source also rates these tumors at 5% in controls of this strain (Greaves and Faccini, *Rat Histopathology*, 2nd Edition, Elsevier, Amsterdam, 1992).

The FDA statistician also found adenoma in female rats to be significantly increased. Using the age-adjusted method, a linear trend was found in the incidence of hepatocellular adenoma in females, $p = 0.008$. Paired comparisons of the control and high-dose groups were not significant. Nor was a combination of adenoma/caarcinoma in males or females significant.

Thyroid follicular cell adenoma in male rats were also found by the sponsor to be significant. The FDA statistician used the age unadjusted method to find a linear trend in the incidence of thyroid follicular cell adenoma, $p = 0.0045$. The age-unadjusted method was used because not all thyroids were available for examination (48, 49, 50 and 46 rats from the male C, L, M and H groups). The combination of thyroid follicular cell adenoma/cystadenoma/carcinoma was also found to be statistically significant in males ($p = 0.0047$). Paired comparisons of the control and high-dose groups were significant for this combination of tumors in the thyroid, but not significant for just adenoma. The historical control rate for thyroid follicular cell adenoma is well below the rate found in this study.

HFD-120 recommended, in 1991, that the sponsor conduct studies to demonstrate that the liver and thyroid tumors found in rats were due to enzyme induction and hormonal effects, as the sponsor claimed. Subsequently, they treated male rats for 14 days with 60 mg/kg/day in the diet and found that microsomal protein increased to 135% of controls on Day 15 when measured as total protein. The activity of the following substances was significantly ($p < .01$) increased in treated rats on Days 5 and 15: cytochrome P450, 180% of controls; 7-EROD, 600% of controls. P-nitrophenol UDPGT was increased on Days 5 and 15 to 170% of controls, ($p < .05$). T_3 and TSH levels in plasma were not affected, but T_4 was 80% of control values ($p < .05$). In a 90-day study using the same dose level, T_4 plasma concentration was not consistently lower in treated rats. TSH was increased in the drug-treated rats by 20-40% on Days 14 and 28, but not Day 92 ($p < .05$). Other rats treated with phenobarbital in this study had reduced T_3 and T_4 levels and increased TSH concentrations, but not at every sampling time (Days 0, 4, 14, 28, 92).

Reproduction Studies

"A Fertility Study (Segment I) with ORG 3770 in Rats"

1. Study Parameters

Test species - Sprague Dawley rats Ico:OFA-SD (IOP Saw) Spf

Supplier -

Body weight - males 53 - 96 g; females 213 - 294 g on arrival two weeks prior to dosing

Route of administration - oral

Vehicle - gelatin (0.5% m/v) and mannitol (5% m/v)

Drug Batch or Lot number - N

Study performed at -

Dates - August - December, 1985

Grouping - 40/s/d

Doses - 0, 2.5, 15, 100 mg/kg

Males were dosed for 9 weeks prior to mating and during mating.

Group A - Twenty females per group were dosed fourteen days prior to mating, during mating and up to and including Day 7 of gestation and were sacrificed on Day 21 of gestation.

Group B - Ten females per group were dosed from fourteen days prior to mating through weaning at Day 21 post partum.

Group C - Ten females per group were dosed from fourteen days prior to mating until Day 13 of gestation, at which time they were sacrificed.

2. Adverse Maternal Effects -

Although all females cycled normally before dosing began, only 37, 38, 19 and 14 of the C, L, M and H groups, respectively, had normal cycles during dosing. The mean duration of the cycle was 4.1, 4.2, 5.3 and 6.7 days in the C, L, M and H groups. In the M group, 13 females had prolonged pro-estrous and 8 had prolonged di-estrous. In the H group, 26 females had prolonged di-estrous.

These effects on cycling did not indicate interference with mating or fertility, as the mean precoital rate was unaffected and those dams that became pregnant all had some live embryos or fetuses upon examination or else had some live young at parturition. There were no drug-related effects on bodyweight.

3. Adverse F1 Effects -

In Group C, the preimplantation loss rate was increased in the L and H groups (8, 24, 14 and 49 %). This effect was significant ($p < .05$) in the L and H groups. Post-implantation

loss was not affected. Preimplantation losses were not significantly affected in Group A.

Neonatal mortality during the first 24 hours after birth was significantly increased in the H group ($p < .05$).

	C	L	M	H
dams with live young	8	6	8	10
# pups at delivery	120	92	106	147
# of pups that died:				
within 24 hrs postpartum	0	2	1	12
in Week 1	5	1	8	8
in Week 2	2	0	0	5
in Week 3	0	0	0	0
mortality within 24 hrs (%)	0.0	2.2	0.9	8.2
mortality after 24 hrs. (%)	5.8	1.1	7.6	9.6

There were no effects on pup weights, malformations, anomalies or other aspects of development except a minor delay in eye opening. Eye opening occurred at means of 16.1, 16.0, 16.6 and 16.8 days for the C, L, M and H groups. The H group was significantly longer ($p < .05$) than the C group, although this probably is not meaningful in a toxicological sense.

Individual data necessary to establish a relationship between cycling and either preimplantation loss or neonatal mortality was not provided.

"A Segment II (Embryotoxicity) Study with ORG 3770 in Rats"

1. Study Parameters

Test species - Sprague Dawley rats Ico:OFA-SD (IOPSaw) Spf

Supplier -

Body weight - females 216 - 313 g on Day 0 of pregnancy

Route of administration - oral

Vehicle - gelatin (0.5% m/v) and mannitol (5% m/v)

Drug Batch or Lot number - N

Study performed at -

Dates - August 86 - January 87

Doses - 0 mg/kg (40 dams), 2.5 mg/kg (41 dams), 15 mg/kg (39 dams), 100 (50 dams) mg/kg

Dosed daily Days 6-17 of gestation. Approximately 20/d were sacrificed on Day 21 of gestation. The remaining dams were allowed to deliver, their litters culled to 4/s on Day 5 pp.

then, after activity and emotionality testing, culled to 3/s. 1/s were then tested for learning & memory and the other 2/s for reproduction testing.

There were only 33, 31, 32, 33 pregnant dams per dose.

2. Adverse Maternal Effects -

Mean weight gain during the first 5 days of dosing was 22, 18, 12, 2 g in the C, L, M and H groups. Only the H group was significantly different from controls. Gains were equal after dosing stopped. Food consumption was decreased in the H group during days 6-10 (75% of controls) but recovered soon thereafter. There were no differences during lactation.

3. Adverse F1 Effects -

Five H dams had resorptions only. Gestation length in that group was 22.7 days compared to 22.0-22.2 for the other groups ($p < .05$). Ovarian weight and preimplantation loss were not affected by mirtazapine, but postimplantation loss was increased in the H group ($p < .01$).

	C	L	M	H
preimplantation loss (%)	13	14	22	2
postimplantation loss (%)	9	6	2	33

The mean fetal weight of H group was 89% of the C group fetal weight ($p < .05$) yet the placental weight was 117% of control ($p < .05$). There were no drug-related anomalies, variants or malformations, no developmental delays, either in morphology or cognitive.

C. An embryotoxicity study with Org 3770 in Dutch rabbits (Netherlands)

A total of 125 spf Dutch rabbits were subdivided as follows:

<u>Group</u>	<u># of Animals</u>	<u>Dose (mg/kg)</u>
C1	25	Untreated
C2	25	Vehicle
LD	25	2.5
MD	25	10
HD	25	40

Org 3770 (batch J) was administered by gavage during days 6-18 of gestation.

Observations:

Daily	Mortality and general condition
Days 0, 6, 12,	Body weights
19, 25 and 29	Food consumption
Day 29	Necropsy
	Reproductive parameters
	F ₁ gross, skeletal and visceral examination

Results:

1. One C2 doe died on day 18 after an intubation error.
2. There were no behavioral signs of toxicity.
3. HD does gained up to 20% less than the C1 group. Body weight gains in other treatment groups were unaffected by Org 3770 treatment.
4. HD food consumption was decreased by 43% during gestational days 19-24 (after termination of Org 3770 treatment).
5. Reproductive parameters are summarized in table 3. Although the rate of postimplantation loss was highest, and fetal weights were lowest in the HD group, the differences from controls were not statistically significant. The number of malformations was also highest in this group. Two types of malformations contributed to the large number of HD malformations, both of which were also prevalent in other groups: pulmonary atelectasis (2, 5, 2, 1 and 5) and missing fifth sternbrae (4, 12, 8, 9 and 21 fetuses from C1, C2, LD, MD and HD groups, respectively). Other malformations were unremarkable in their distribution among treatment groups, and included small size (0, 2, 1, 3 and 2), spina bifida (2, 0, 2, 1 and 0), cleft palate (0, 1, 0, 1 and 2), brain malformations including hydrocephalus (2, 5, 2, 1 and 5) and misshapen ribs (0, 0, 2, 0 and 3 fetuses from C1, C2, LD, MD and HD groups, respectively). The overall incidence of skeletal and visceral variations was also unremarkable. These were found in 93-100% of examined fetuses. However, the distribution appeared to be altered slightly, so that ossification delays appeared to be more prevalent in Org 3770-treated litters.

Table V - Reproductive Parameters

	C1	C2	LD	MD	HD
# Pregnant does	15	19	22	23	22
# w/Live fetuses	14	18	21	22	21
# w/Abortions or dead fetuses only	1	1	1	1	1
# Corpora lutea	6.33	6.78	7.09	7.39	7.09
# Implantations	5.33	6.21	6.18	5.78	6.36
# Viable fetuses	4.66	5.05	5.18	5.08	4.90
* Postimplantation loss	12.6	18.7	16.2	12.1	23.0
Fetal wt (g)	37.5	37.4	39.5	39.6	37.0
Sex ratio (M:F)	1.15	1.27	1.15	0.87	1.06
# Malformations	4	10	9	11	20

"A Segment III (Peri- and Post-Natal) Study with ORG 3770 in Rats"

1. Study Parameters

Test species - Sprague Dawley rats Ico:OFA-SD (IOPSaw) Spf

Supplier -

Body weight - females 214 - 343 g on Day 0 of pregnancy

Route of administration - oral

Vehicle - gelatin (0.5% m/v) and mannitol (5% m/v)

Drug Batch or Lot number - N

Study performed at -

3

Dates - August 1986 - April, 1987

Grouping - 40/s/d

Doses - 0 mg/kg (22 females), 2.5 mg/kg (25 females), 15 mg/kg (22 females), 100 mg/kg (25 females)

Females were dosed from Day 17 of gestation up to and including Day 28 of lactation.

"At day 5 postpartum the litters were reduced to 4 males and 4 females. After completion of the test for activity and emotionality 3 male and 3 female animals from each litter were maintained for further testing and crossing. The remaining animals were sacrificed (around day 35 postpartum)."

"At weaning, two F1 females and two F1 males from each litter were taken in a non-selective way for further breeding. At about week 10 of age the females and males from different litters of

the same test group were caged together on a one-to-one basis. After successful mating both female and male remained in the same cage until Day 14 of pregnancy."

2. Adverse Maternal Effects -

Weight gain between Days 17 and 21 of gestation were 55, 50, 42, and 8 for the C, L, M and H groups respectively. The H group was significantly different from the control group ($p < .05$). The H dams gained more during the lactation period and caught up to controls by the end of lactation. Food consumption was reported only for Days 0-16 of gestation, during which time no drug-related effects were noticeable.

Seven high-dose litters were entirely lost before birth. One H dam was autopsied on Day 23 of pregnancy and all embryos had resorbed. One dam delivered prematurely on Day 20 and three others on Day 21 of gestation. All their fetuses were dead. Two other H dams had all dead fetuses at delivery on Day 23. Only one control dam lost an entire litter. This was a case of resorptions found on autopsy on Day 24 of gestation. Gestation length was not affected by the drug.

3. Adverse F1 Effects -

The sponsor stated that "Neonatal mortality within 24 hours and after one week post partum was significantly increased in the high dose ORG 3770-treated group". The figures below do not include the lost litters cited above in the maternal effects section.

	C	L	M	H
dams with live young	19	20	20	16
# pups at delivery	230	275	263	230
# of pups that died:				
within 24 hrs postpartum	2	9	4	20
24-72 hrs	0	8	3	29
Days 4-7	0	1	2	4
in Week 2	0	2	0	8
in Week 3	0	0	1	1
in Week 4	0	0	0	1
mortality within 24 hrs (%)	0.9	3.3	1.5	8.7
mortality Days 2-7 (%)	0.0	3.3	1.9	18.7
mortality after Week 1 (%)	0.0	0.7	0.4	4.3

* the litters were culled on Day 5 to 4/sex/litter.

F₀ LITTER DATA

Group		1 control	2	3	4
Dose (mg/kg/day)		0	2,5	15,0	100,0
No. of animals	with live young	19	20	20	16
	with embryonic death only	1	0	0	1
	which aborted ^x	0	0	0	6
Gestation length (days)		22,4	22,4	22,2	22,4

F₁ GENERATION

No. of young	alive at delivery	230	275	263	230
	which died within 24 hrs post partum	2	0	4	20
	which died after 1 week post partum	0	2	1	10
Body weight (g)	at start of lactation	6,6	6,4	6,2	5,0
	after 4 w of lactation	99,9	92,0	92,0	75,6
	at start of weaning ♀	96,4	87,6	88,7	74,3
	6 w after weaning ♀	239,3	231,1	227,3	208,3
	at start of weaning ♂	103,2	102,4	94,9	78,5
	6 w after weaning ♂	376,4	374,2	364,0	317,1

MATING AND PREGNANCY PERFORMANCE F₁ GENERATION

Mating rate (%)		100,0	89,2	100,0	100,0
Pregnancy rate (%)		94,1	100,0	94,1	95,7
Pre-ovital interval (days)		2,9	2,5	2,5	2,6
No. of animals	pregnant	32	33	32	22
	non-pregnant	2	0	2	1
	with live embryos	32	33	31	22
	with embryonic death only	0	0	1	0
No. of	corpora lutea	302	337	303	311
	implants	490	513	487	297
	live embryos	457	496	461	285
	embryonic death	33	17	26	12

^x including premature delivery and delivery failure

It appears that the dams that lost more than 2 pups within the first week after birth were these:

002,
003,
016,
023

The dams that lost weight during the first week of dosing were these¹:

002
003
010
015
022

¹ These do not include those that lost their entire litters before birth as cited above in maternal effects

After studying the above listings, one is not required to conclude that losing weight during pregnancy contributed to the early death of pups.

Pup weights of the high-dose group were only 75% of those of the control group ($p < .05$) at the start of lactation and remained that way throughout the 28 day lactation period. The low- and mid-dose groups were about 8% less than controls during lactation. However, after that time, the remaining pups that were to be used in further developmental tests were not different from controls in bodyweight. Yet, at Day 0 of pregnancy for the F1 females bred, the high-dose group bodyweights were only 87% of the control group weights. This difference was maintained through the 14 days of gestation until they were all sacrificed.

The H dams that lost weight during the first week of dosing were not necessarily those that had low birth weight pups. Dams 002, 003, 024 had mean pup weights of 4 g at birth. Most other dams had mean pup weights of 5 g and three had 6 g.

There were no drug effects on developmental measures, other than bodyweight.

DEVELOPMENTAL AND BEHAVIORAL DATA F_1 GENERATION

Group		1 control	2 low	3 mid	4 high
Dose (mg/kg/day)		0	2,5	15,0	100,0
Mean day post partum of ^a	vaginal opening	34,6	34,1	34,3	35,6
	pinna unfolding	2,6	2,7	2,7	2,9
	eye opening	14,7	15,0	15,0	14,8
	static righting	2,4	2,7	3,1	4,0
	air drop righting	16,4	17,0	16,4	17,7
	negative geotaxis	8,7	9,1	8,2	9,5
	Irwin assessment (mean litter score)	11,3	22,6	22,4	23,2
	Auditory response (ratio)	1,1	1,3	1,5	1,97
	Rotarod performance (mean litter score in sec)	14,4	74,7	85,2	86,2
Activity and emotionality ^b	No. of defecations	0,9	1,4	1,42	1,26
	No. of rearings	14,3	12,1	10,8	11,5
	No. of starts	25,0	23,1	24,1	22,9
	Moving time in sec	90,4	94,3	93,1	98,5
	Average speed in cm/s	16,5	16,8	16,4	17,7
	Average distance run in cm	1501	1606	1634	1774
Learning and memory	day 1				
	Intertrial responses	27,8	29,6	26,3	34,5
	Avoidance	5,2	5,9	5,1	5,6
	Escapes	10,0	9,5	10,0	9,6
	Latency time	123	124	130	132
	day 7				
	Intertrial responses	39,2	35,3	34,4	40,4
	Avoidance	11,3	10,6	11,7	11,0
	Escapes	4,7	5,3	4,3	5,0
	Latency time	62	68	61	66

^a day on which the total litter scores positive ^b mean per litter

Special Studies - Genotoxicity Tests

A. Unscheduled DNA synthesis (UDS) in HeLa S3 cells in vitro

Org 3770 was tested at concentrations of 4-800 $\mu\text{g/ml}$ for genotoxic activity (induction of unscheduled DNA synthesis) in cultured human cells. No activity was found at concentrations of up to 400 $\mu\text{g/ml}$, with and without metabolic activation (rat S9 mix). Marked toxicity to cells was evident at higher concentrations.

B. Gene mutation in Chinese hamster V79 cells

Org 3770 was tested for mutagenic activity at concentrations up to 400 $\mu\text{g/ml}$. There was no evidence of reversion to 6-thioguanine sensitivity at Org 3770 concentrations of up to 300 $\mu\text{g/ml}$, with and without metabolic activation (rat S9 mix). Higher concentrations were cytotoxic.

C. Micronucleus test in rats with Org 3770

Rats (6/sex) were dosed with Org 3770 (1, 10 and 100 mg/kg i.g. x 2 days) followed by sacrifice. Marrow smears were examined microscopically for the presence of micronuclei. Org 3770 showed no evidence of clastogenic activity.

D. A *Salmonella* microsome mutagenicity test (Ames test) with Org 3770

Org 3770 was tested at concentrations of 8-5000 $\mu\text{g/plate}$ in the test strains TA98, TA100, TA1535, TA1537 and TA1538 with and without metabolic activation. No evidence for a change in the rate of reverse mutations was found after treatment with Org 3770.

E. A sister chromatid exchange test in rabbit lymphocytes in vitro with Org 3770

Rabbit lymphocytes in primary culture were incubated with Org 3770 (37-300 $\mu\text{g/ml}$) with and without metabolic activation (rat S9 mix), followed by assay for sister chromatid exchanges during metaphase. Org 3770 displayed no clastogenic activity in this assay.

Special Studies - Metabolism Effects

Hepatic enzyme induction studies of Org 3770 and mianserin in the male mouse

Male CD-1 mice were administered Org 3770 (200 mg/kg) or mianserin (240 mg/kg) in the diet for 4 or 28 days. The following hepatic parameters were measured: microsomal and cytosolic protein, microsomal P450, activities of p-nitrophenol-glucuronyl-transferase (NGPT), AH, AND, ECOD and glutathione S-transferase. Treatment with Org 3770 for 4-28 days led to increases in hepatic protein (11-36%), P450 (32-58%), AH (32-67%), AND (56-86%), ECOD (132-193%) and glutathione S-transferase (28-57%) activities. NGPT activity was unaffected. These changes were comparable to those observed after mianserin treatment.

Enzyme induction and its reversibility in liver of rats after repeated oral administration of Org 3770

Male and female WISTAR rats were treated with Org 3770 (80 mg/kg i.p.) or phenobarbital (80 mg/kg i.p.) for 4 consecutive days, after which they were sacrificed. The following hepatic parameters were tested: weight, protein and P450 content, 7-ethoxycoumarin-O-deethylase (ECOD), aminopyrine-N-demethylase (AND) and aniline-hydroxylase (AH) activities (females only). Treatment with Org 3770 produced induction of hepatic P450 activity equivalent to that elicited by the positive control, phenobarbital, as evidenced by increases in liver weights (17-31%), P450 content (15-46%), ECOD (169%), AND (115%) and AH (42%) activities. The changes in hepatic weights, protein and P450 content were generally greater in females compared to males. All parameters had returned to baseline within 4-8 days.

"ORG 3770: Effect on Selected Hepatic Drug Metabolising Enzymes and Thyroid Function in Male Rats Following Dietary Administration for 2 Weeks"

Twenty-seven Sprague Dawley CD rats were given the drug in the diet at a dose level of 60 mg/kg/day for 14 days. Twelve other rats served as controls and were not dosed. Of the 27 treated rats, 18 were used only for sampling plasma levels of the drug, but the results of this analysis were not submitted. 3 of the remaining 9 treated animals were sacrificed on Day 4 of the study (along with 6 controls) and the remaining 6 treated animals had blood drawn on Days 1, 4, 7, and 14 for the measurement of thyroid hormones (T_3 , T_4 , TSH) and were then sacrificed on Day 15. The liver, thyroid and pituitary of each sacrificed rat were weighed. The livers were then subjected to analysis for microsomal protein, cytochrome P450, p-nitrophenol UDP-glucuronyltransferase (PNUDP), and 7-ethoxyresorufin O-deethylase (7-ERD).

RESULTS

1. Weight gain in the treated rats was only 85% of the control rats, but this difference was not statistically significant. Food consumption in the treated rats was 119% of controls ($p < .01$), thus food utilization was less efficient in the treated animals, suggesting that general metabolism in the treated rats was greater than that in the controls.

2. T_3 and TSH levels were not different than controls, but T_4 levels were 84% of controls throughout the study, even on Day 1 ($p < .05$).

3. Liver weights of the treated rats were 109% of controls ($p < .05$), but pituitary and thyroid weights were not affected by the drug.

4. Microsomal protein was increased in treated rats to 135% of controls on Day 15 when measured as total protein. The following substances were significantly ($p < .01$) increased in treated rats on Days 5 and 15: cytochrome P450, 180% of controls; 7-ERD, 600% of controls. PNUDP was increased on Days 5 and 15 to 170% of controls, ($p < .05$).

"A 90-Day Thyroid Function Study in Male Sprague-Dawley Rats with ORG 3770"

ORG 3770 was given to 50 rats at 60 mg/kg in the diet and fifty others received it via gavage. 50 were controls and 50 others received phenobarbital at 75 mg/kg via gavage. Ten rats/group/interval were sacrificed on Days 0, 4, 14, 28 and 92. Liver and blood samples were collected.

Liver weights of ORG 3770-treated rats were slightly greater than controls, but the differences were not significant. Pheno-treated rats had significantly heavier liver weights, absolute and relative, up to 118% of controls. Mean thyroid/parathyroid weights of diet ORG 3770-treated rats were 125% of controls on Day 14 (absolute, $p < .05$) and Day 92 (relative, $p < .05$). The means for Days 28 was 110% of controls ($p > .05$). Gavage-treated rats did not differ from controls. Pheno-treated rats had heavier thyroids on Days 14 and 92 ($p < .01$).

TSH was increased in the rats given ORG 3770 via gavage or diet by 20-40% on Days 14 and 28. Statistical significance was not reported for hormone levels in this study. The rats were tested at BioDynamics in NJ and the blood analyzed by Braverman and DeVito at the Massachusetts Medical School in Worcester, MA. The TSH increases on Days 14 and 28 appear to me to be real differences, but this effect was not present on Day 92. T_3 concentrations of diet-ORG 3770-treated rats were claimed by the researchers to be lower than controls on Day 4. The means of these two groups were 110 ng/dl for the controls and 97 for the ORG 3770 diet-treated group. However, these two groups had means of 155 and 112 before treatment began, so this is probably not a drug effect. There were no other signs of an effect on T_3 . T_4 plasma concentration was not consistently affected in treated rats. The largest difference between controls and diet-treated rats was on Day 28 when the ORG rats had levels that were 127% of controls, but this difference is not likely to be statistically significant due to large variances within each group. Other rats treated with phenobarbital in this study had reduced T_3 and T_4 levels and increased TSH concentrations, but not at every sampling day. Generally, the effects of the phenobarbital were slightly greater than those of ORG 3770. The increases in TSH,

generally seen in the three treated groups on Days 4, 14, or 28, were the largest changes of all three hormones measured.

Special Studies - Cardiovascular Toxicity

Investigation on cardiotoxicity of Org 3770, mianserin and imipramine in anesthetized dogs

Cardiotoxicity following overdosage of imipramine, mianserin or Org 3770 was assessed in chloralose-anesthetized, ventilated beagle dogs. Drugs were infused i.v. at a rate of 30 mg/kg-hr (5 animals/drug) for a maximum of 5 hr or until animals died from cardiac arrest. Blood pressure, cardiac output, ECG and other cardiovascular parameters, as well as plasma drug levels were monitored.

Of the dogs dosed with Org 3770, 4/5 died just prior to the end of the experiment; the remaining animals survived. The average cumulative Org 3770 dose was 138.6 mg/kg. This dose produced peak plasma drug levels which fell within the range of 7-20 $\mu\text{g/ml}$. In the mianserin group, 3/5 animals survived, while the other 2 died near the end of the infusion period. The average cumulative dose was 144.5 mg/kg and the maximum plasma concentration was in the range of 8-16 $\mu\text{g/ml}$. In contrast, all 5 of the imipramine animals died from cardiac arrest during the first 3 hr of infusion. The average cumulative dose was 64.3 mg/kg which corresponded to maximum plasma levels in the range of 4-11 $\mu\text{g/ml}$.

Aside from exceptions listed below, changes in cardiovascular parameters were generally comparable in the 3 experimental groups, with the changes occurring earlier (at ~50% lower plasma levels) in the imipramine group. These changes included decreased heart rate (up to -100 bpm), decreased arterial blood pressure (systolic -75-100 mmHg, diastolic -50-75 mmHg), decreased left ventricular Vmax and dP/dt, decreased stroke volume and cardiac output (~1 l/min), and increased right atrial pressure (+5-10 mmHg systolic and diastolic). Total peripheral resistance was generally unaffected. Imipramine produced an initial 50 bpm increase in heart rate and a slight increase in cardiac output, followed by a gradual cardiodepressant effect. In addition, LVEDP was increased by 10 mmHg in the imipramine group only. Blood gases and hematologic parameters were generally unremarkable. The changes in cardiovascular parameters were correlated to plasma drug concentrations and formed an overall picture of a gradual decrease in left ventricular contractility, leading to a decline in stroke volume and cardiac output. The resulting decrease in blood pressure led to insufficient perfusion pressure and cardiogenic shock.

ECG revealed 30-50% increases in PQ intervals for all groups, and a 25% increase in QT interval which was seen only in the mianserin group when values for corrected for heart rate changes. The QRS interval was increased by 10-25% in the imipramine and mianserin groups only. All of the ECG changes were most evident near the end of the infusion, coincident with the onset of shock.

Summary

Org 3770 (mirtazapine) is an antidepressant which is structurally related to mianserin and to ORG 4428 which is now undergoing clinical testing as an antidepressant (IND 39,520). ORG 3370 is a racemic drug which appears to display antagonist activity at serotonergic 5-HT₂ and noradrenergic α_2 receptors, but also displays moderate antagonist activity at histaminergic H₁ and 5-HT₁ receptors. It appears to be weak or inactive at cholinergic and dopaminergic receptors. Unlike most antidepressants, Org 3770 does not act as an uptake inhibitor for monoamine neurotransmitters.

Organon generally feels that NE activation is an effective remedy for depression. It is likely that NE activation is the strongest effect of this drug, relative to serotonergic effects. Org 4428 is a selective NE reuptake inhibitor.

Remarkably, some of the receptor blocking properties of mirtazapine were noted for the racemic mixture and only one or the other of the two enantiomers, or, with just one enantiomer and not the racemic mixture.

CNS-pharmacological profile of ORG 3770 and its enantiomers

CNS-Pharmacological Profile	ORG 3770	(S)+enant.	(R)-enant.
<u>Behavioral models</u>			
Antidepressant-like effects			
- bulbectomized rat: behavioral	+	+	-
biochemical	+	-	+
- acquired immobility test	-	-	+
Anti-anxiety effects			
- anxiousity test	±	±	±
<u>EEG-studies</u>			
Antidepressant profile			
- sleep (rat)	+	+	±
- sleep (human)	+	+	+
<u>Receptor interactions</u>			
Noradrenaline (α_2 -blockade)			
- enhancement NA release	+	+	-
- rauwolscine displacement	+	+	-
- antagonism clonidine mydriasis	+	+	-
Serotonin			
- affinity 5HT ₂	+	+	±
- affinity 5HT ₃	+	-	+
Histamine			
- H ₁ -antagonism	+	+	+
Acetylcholine			
- QNB binding	-	-	-
- guinea-pig ileum	-	-	-

ORG 3770 increased the potassium-induced release of NE in an in vitro preparation and also displaced rauwolscine (an α_2 antagonist). In vivo, it antagonized mydriasis induced by clonidine, an α_2 agonist. These effects suggest that it would increase NE tone centrally as well as peripherally by blocking presynaptic α_2 receptors, thereby releasing more NE. It may also increase serotonergic tone because α_2 receptors are also located on 5-HT nerve terminals (idazoxan, an α_2 antagonist, increases release of 5-HT). Its 5-HT₂ antagonism may help relieve neurotic aspects of some depressed patients and its 5-HT₁ antagonism may relieve anxiety associated with depression. There is some weak α_1 antagonism, as shown by pA₂ values of 6.2 for the parent and a metabolite, Org 3838, in the rat vas deferens contraction test. ORG 3770 not only binds to H₁ sites in in vitro binding studies, but it acts at those sites in guinea pig ileum. This effect is probably responsible for sedation occurring in some patients. It was completely inactive at H₂ sites. In addition to having only

very weak binding at muscarinic receptors, it did not antagonize the effects of tremorine in the guinea pig ileum.

The sponsor pointed out that the structure and mechanism of action of ORG 3770 is different from that of more traditional antidepressants which block the reuptake of monoamines, such as the tricyclics and the new SSRI's, and therefore should not be expected to be positive in every model of depression because some models were developed for specific classes of drugs based on mechanisms of action. ORG 3770 lacked activity in some classical models of antidepressant efficacy. The racemate and the (+) enantiomer were inactive in the forced swim, or as the sponsor calls it, the acquired immobility, test. Curiously, the (-) enantiomer did delay the onset of immobility. No explanation was given for this phenomenon.

The sponsor's own scientist, J. S. de Graaf, developed a test for antidepressant efficacy in which the natural predatory behavior of rats toward mice is measured. But when ORG 3770 was tested, it did not influence predatory behavior. In a related test, mice treated with ORG 3770 decreased aggression induced by isolation (ED_{50} = 5 mg/kg p.o.), suggesting that this drug would be an effective antidepressant. Finally, the drug did prove to be effective in the olfactory bulb-ectomized rat model of depression. In this test, the racemate (at doses of 0.5 and 1.0 mg/kg, sc) and the (+) enantiomer (at doses of 1 & 2 mg/kg, sc) blocked the hypermotility in the open field induced by bulbectomy. The (-) enantiomer was not effective. At higher doses, the racemate induced sedation, indicated by reduced numbers of crossings in the open field. These rats were treated with the drug for 12 consecutive days before testing began. This particular test is valid only with subchronic dosing (with any drug, not just ORG 3770), i.e. acute dosing has no effect on the hypermotility. Bulbectomy reduces the NE and MHPG content of the amygdaloid cortex and the midbrain. Treatment with ORG 3770 reversed this effect, probably by blocking α_1 receptors.

ORG 3770 produced an "antidepressant" profile in healthy human volunteers. It also affected EEG sleep patterns in rats in a manner similar to that of classical and atypical antidepressants. At 1 mg/kg ip, it reduced waking and increased deep sleep without affecting REM sleep. At 3.2 mg/kg, it increased deep sleep and reduced REM with no other effects. Finally, at 10 mg/kg, it suppressed deep sleep and REM resulting in increased quiet waking behavior.

The sponsor is suggesting that this drug will also act as an anxiolytic, based on its effect in the "anxiolytic" test. This test is the punished drinking conflict test in which rats are water-deprived and then electrically shocked when they lick the drinking tube. ORG 3770 was only mildly effective at increasing punished drinking at doses of 1-2 mg/kg and appeared to be less efficacious than benzodiazepine-like anxiolytics.

Demethyl ORG 3770 is the only metabolite that was found in the brain and the only one to be tested for activity. It was

found to be less active than the parent in the EEG antidepressant profile study and in vivo antagonism of α_2 , 5-HT₂, and H₁ receptors. These differences may be due only to relatively poor bioavailability of the metabolite compared to the parent drug, because receptor binding studies did not indicate a difference between the metabolite and the parent. The 8-hydroxy, 8-hydroxy demethyl, and the N(2)-oxide metabolites were less active than the parent in in vitro activity tests. No other metabolites were tested.

The cardiovascular pharmacology of ORG 3770 was studied in conscious rabbits, anesthetized cats and dogs. Blood pressure and heart rate were not affected at doses up to 1.0 mg/kg i.v., except for slight decreases in heart rate in the dog at 1.0 mg/kg. These dogs also exhibited slightly decreased myocardial contractility and slightly increased peripheral resistance at that dose. At 10 mg/kg i.v., the same effects were noted in dogs as at the lower dose of 1 mg/kg, but in cats, the dose of 10 mg/kg i.v. slightly lowered heart rate and blood pressure, which it had not done at lower doses. Also, the highest dose of 10 mg/kg reduced the changes resulting from vagal stimulation and carotid occlusion, and, in rabbits, from NE and isoprenaline. The drug itself never affected pressure or rate in conscious rabbits.

PK

The drug is rapidly absorbed in rats (< 30 min) and in dogs (1-1.5 hrs). After i.v. administration, the distribution phase half-life was 12 min in rats and 24 min in dogs. The second phase (elimination) half-life lasted for 2-3 hrs in these species. It has a modest volume of distribution in the rat (4-5 l/kg) but quite large in the dog (20 l/kg). Radiolabel studies indicated penetration of ORG 3770 and its metabolites into most body tissues, including the brain, but no evidence of drug accumulation. Only the parent drug and its N-desmethyl metabolite (possibly active) were found in the brain.

ORG 3770 is a substrate for microsomal oxidation. In the species tested (rat, rabbit, mouse, guinea pig, dog and man), ORG 3770 was subject to N-demethylation and 8-hydroxylation followed by formation of glucuronide and sulfate conjugates. Approximately one-third of the radioactivity in a dose was excreted in urine and slightly more than one-half in feces. Although the drug did not accumulate in plasma, the tissue:plasma ratio of brain, eyes, skin, heart and lung doubled after multiple dosing. ORG 3770 is bound to plasma proteins to a moderate degree (85%). These binding sites should not be saturated in the physiological range of plasma drug concentrations. The drug induces hepatic P450 (evident by changes in liver weight, P450 content, and oxidating activity) in mice and rats and thus should tend to speed its own and other drugs' metabolism (see further summary of enzyme induction under toxicity section). In rats, the drug crosses the placental barrier and is found in milk.

Toxicology

Acute toxicity studies were carried out in mice and rats. The LD₅₀ values for orally administered ORG 3770 were 810 and 720 mg/kg for males and females, respectively. In rats, the oral LD₅₀ values were 490 and 320 mg/kg, males and females respectively. When ORG 3770 was administered intraperitoneally to rats, the LD₅₀ values were slightly greater than 100 mg/kg. The two enantiomers of ORG 3770 each had oral LD₅₀ values of slightly greater than 200 mg/kg. These studies were not GLP, but the most significant discrepancy from GLP was the fact that the potency of the drug was not analyzed.

Chronic Toxicity Studies

Thirteen-week toxicity studies were reported for rats and dogs, but since the high doses used in these studies were the same as the high doses used in one-year studies in rats and dogs, they are not reviewed here. However, gavage dosing was used in the shorter study and dietary admixing in the longer rat study. Both dog studies utilized capsule/tablet dosing on a daily basis. Also, these studies are not reviewed because they were not GLP. According to the sponsors summaries of those studies, the findings do not differ from those of the one-year studies.

In one-year studies, rats were administered ORG 3770 in the diet at doses of 2.5, 20, and 120 mg/kg/day and dogs by tablet at doses of 2.5, 15, and 80 mg/kg. There were no behavioral findings for rats and were only transient in dogs, including inappetence, emesis and tremor, as well as a single episode of tonic/clonic convulsions in 1 HD dog.

The drug caused animals in the high dose groups to gain significantly less weight than controls. HD rats weighed only 33% of controls and HD dogs were 7-20% less than controls. Although both species had weight decrements, HD rats ate more food than controls and dogs ate the same or slightly less than controls. The lower dose groups helped form a dose-related trend, but were not significantly different from controls. The structurally similar ORG 4428 also stimulated increased food consumption in rats while producing severe weight decrements.

HD dogs experienced a mild normochromic, normocytic anemia, and elevated serum alkaline phosphatase and transaminase activities. The sponsor attributes the former change to decreased food consumption and the latter to a generalized induction of hepatic microsomal enzyme activity by ORG 3770. Recovery values for these hematologic and clinical chemistry values were normal. There were no significant changes in differential leukocyte counts. There were no unusual blood

findings in rats. Thus, neither of these studies predicted the 3 cases of agranulocytosis encountered in clinical trials.

Autopsy findings in the dog study included increased liver weights with hepatic enlargement and hypertrophic changes consistent with enzyme induction. Again, recovery was complete after 5 weeks of washout. HD rats had relative liver weights that were significantly ($p < .01$) greater than controls, but there was no mention of hypertrophy after microscopic examination of the liver.

Microscopic renal changes were found in HD rats, mostly males. There was greatly increased numbers of vacuoles in the cytoplasm of tubular epithelial cells. This was not accompanied by necrosis or degeneration, although mild pigmentation in these cells may indicate that some organelles were compromised. Some recovery was noted after one month. The same effect was noted in the 13-week study. These findings were not replicated in the dog, although dogs did have evidence of slight renal inflammation.

Carcinogenicity Mice were tested for 18 months at doses of 2, 20 and 200 mg/kg in the diet. Rats were tested for 24 months at doses of 2, 20 and 60 mg/kg in the diet. The drug had no effect on mortality in mice. There was a significant linear trend ($p = 0.0038$) for survival in male rats, indicating that the drug decreased mortality in the high-dose group (percent survival after 24 mos. in controls = 30, in high-dose males = 56). The drug had no effect on mortality in female rats.

The terminal sacrifice body weights of male mice were 6% lower than controls and females were 4% less than controls. Neither group was significantly different from the respective control group. With a large number of mice still alive in each group ($n = 26-31$), it could be expected that even these small percentage differences should be significant, but they weren't. Increased food consumption by treated mice, compared to controls, probably helped keep bodyweight decreases to a minimum and suggests that general metabolism may have been increased in the high dose group. Food utilization in drug-treated rats was also poor, especially in females. High-dose females ate 130% as much food as controls, but their body weights were only 71% of controls. Mid-dose females ate 111% as much as controls but weighed only 86% of controls. Male body weights for the L, M and H groups were 94%, 87% and 76% of controls and their food consumption was 104%, 105% and 111% of controls, respectively.

Differential leucocyte counts were taken in both mice and rats, but no relationship to the drug was found. Gross and histopathological lesions, other than the tumors reported herein as statistically significant, were of the type normally

encountered in aged rodents and were not related to drug treatment. However, there appeared to be a trend toward elevated uterine tumors and increased cervical hyperplasia in females dosed with 60 mg/kg. Although not statistically significant, this could be indicative of an endocrine disturbance not previously detected.

There were no single tumor types in mice that were statistically significant, but when hepatocellular adenoma and carcinoma were combined, there was a linear trend in male mice (7, 5, 11, 17 in C, L, M, H groups; $p = 0.0015$). The incidence, in male mice, of adenoma was 3, 3, 6, 10 and of carcinoma was 4, 2, 5, 8. One HD mouse had both one adenoma and one carcinoma. The number of mice with liver masses or nodules increased in a drug-related manner. Male mice had increased activity of liver enzymes, including P450. There was also ultrastructural evidence of induced enzyme activity in the form of modestly increased smooth endoplasmic reticulum in males of the high-dose group.

Male rats had an apparent, but not significant, increase in hepatocellular adenoma (0, 0, 0, 3 in C, L, M, H groups). Female rats had a significant increase in hepatocellular adenoma (0, 0, 4, 5; $p = 0.008$, trend test). A paired comparison of the control group with the high-dose group was not significant. When this type of liver tumor was combined with hepatocellular carcinoma for statistical analysis by the FDA statistician, the combination was not significant in either sex. Although the p values for these analyses were 0.0101 for males and 0.0077 for females, they are not considered significant after correction for multiple tests of common tumors. The number of rats with hepatocellular adenoma in this study is within the range of historical controls. However, the occurrence of adenoma was only in the groups treated with higher doses of the drug. Carcinoma was also within the range of historical controls, but occurred in all treatment groups and the control group.

Male rats had a statistically significant increase in thyroid follicular cell adenoma/cystadenoma (1, 4, 5, 9 in C, L, M, H groups; $p = 0.0045$, trend test). When these tumors were combined with thyroid follicular carcinoma (0, 1, 1, 3), the result was also significant, $p = 0.0047$. Neither tumor type alone or the combination were significant in female rats.

Three reproduction studies were carried out in Sprague-Dawley rats using doses of 0, 2.5, 15 and 100 mg/kg. Dutch rabbits were dosed with 0, 2.5, 10 and 40 mg/kg in a Segment II study. The weight gains and food consumption of high-dose dams and does were reduced relative to controls. Oddly, the rabbits drastically reduced food consumption by 43% AFTER dosing stopped. High-dose rats resumed food consumption and weight gain at normal or

supranormal levels a few days after the initiation of dosing. Mid- and high-dose females in the Segment I study had prolonged pro- or diestrous prior to mating, but this did not interfere with mating.

Three different dosing regimens were used in the Segment I study. All started dosing 14 days prior to mating, but dosing was terminated on Day 7 of gestation, Day 13 of gestation, or Day 21 pp. Preimplantation loss was increased in the low- and high-dose groups (24 and 49%; $p < .05$) of those dosed until Day 13 of gestation and then sacrificed at that time. Preimplantation losses were not affected by the drug in the other dosing regimens. The number of pups/litter was not affected by the drug in the group allowed to deliver. Postimplantation loss was not affected in any of these groups of the Segment I study, but were significantly affected in the Segment II rat study and there appeared to be an insignificant increase at the high dose of the rabbit study. Postimplantation loss in the high-dose rat group (Segment II) was 3-4x that of the other groups, $p < .01$. There were no signs of teratogenicity in the rat study and only very weak signs in rabbits, namely a possible slight increase in F_1 findings of pulmonary atelectasis and missing fifth sternbrae. Both of the latter findings may be considered as manifestations of embryotoxicity which are secondary to growth retardation.

Pup mortality was a major finding in the Segment III study and was also significantly increased in the Segment I study. The percentages of pups dying within the first 24 hrs of the Segment I study were 0, 2, 1, 8 for the C, L, M, and H groups, respectively. During the next 3 weeks, pup mortality continued to be greater in the high-dose group, although the differences were not so dramatic as in the first 24 hrs. In the Segment III study, 7 entire litters in the high-dose group were lost at or before birth. No other dams lost litters. The sponsor did not count any pups as "stillborn". Of those born alive, 1, 3, 2 and 9% (C, L, M, H) died within the first 24 hrs and an additional 0, 3, 2, and 19% died during the 2nd and 3rd days after birth. There was no correlation of the reduction of dam body weight gain during gestation with pup mortality.

Pup body weights of the high-dose group were only 75% of the control group weights at birth and did not recover during lactation. Birth weight did not correlate with dam reduced weight gain. Birth weights of the low- and mid-dose groups were only 92% of the control group weights.

A series of five mutagenicity screens (Ames, sister chromatid exchange, in vivo rat micronucleus, gene mutation in Chinese hamster V79 cells, and unscheduled DNA synthesis) failed to detect clastogenic or mutagenic effects of ORG 3770.

Male mice given ORG 3770 at 200 mg/kg in the diet (as in the carcinogenicity study) for 4 and 28 days were found to have increased hepatic protein (11-36%), P450 (32-58%), aniline hydroxylase (32-67%), aminopyrine-N-demethylase (56-86%), 7-ethoxycoumarin-o-deethylase (132-193%) and glutathione S-transferase (28-57%) activities. p-Nitrophenol-glucuronyl-transferase activity was unaffected.

The sponsor then tested male rats for liver enzyme activity and found increased P450, 7-ethoxyresorufin-O-deethylase, and UDP-glucuronyltransferase activity.

T₄ levels in plasma were found, in a subsequent study, to be lower in rats treated with the high-dose used in the carcinogenicity study, than in controls, but TSH levels were not affected by the drug. In yet another study, TSH levels were found to be elevated during the first month of treatment, but not after 3 months. T₄ levels fluctuated above and below the levels of controls.

In a study of cardiovascular safety, ORG 3770 was compared to mianserin and the tricyclic antidepressant, imipramine. The cardiotoxicity safety index for both ORG 3770 and mianserin was approximately twice that of imipramine when equal doses were tested, whereas the ratio was much higher when therapeutically equivalent doses were tested. Thus, ORG 3770 required high doses (> 100 mg/kg i.v.) to produce cardiovascular toxicity, manifest as cardiodepression leading to shock. Electrocardiographic changes were evident only at doses which decreased myocardial perfusion. Thus, direct effects on cardiac conduction do not appear to be a toxic effect of ORG 3770 treatment, as they appear to be with tricyclic antidepressants.

EVALUATION

Mouse Carcinogenicity Study The slight weight reductions in high-dose mice suggest that the dose of 200 mg/kg was close to the MTD. The increased food consumption stimulated by the drug may have prevented greater weight disparities in these mice. This drug did not increase mortality or cause any form of pathology except to stimulate liver activity. Therefore, the high-dose of 200 mg/kg could be accepted as the MTD for mice. Dose-range-finding studies were not submitted with this NDA. It would be appropriate for the sponsor to justify their selection of 200 mg/kg as the high-dose. If the justification is not sufficient, the labeling proposed herein may need to be modified.

Hepatic microsomal induction is an accepted nongenotoxic mechanism by which certain tumor types may be increased in animals. Thus, hepatic tumors may be induced in mice by known inducing agents (e.g. phenobarbital, benzodiazepines) and the background incidence of these tumors is high, at least in some strains (e.g. male B6C3F1 mice). Therefore, the mouse tumor data in the present study are not particularly disturbing for the following reasons: (1) mutagenicity studies indicate no direct ORG 3770 genotoxicity, (2) hepatic microsomal induction has been demonstrated in this and other species, and (3) the liver tumors were restricted to a single sex (males) and dosage group. Nevertheless, the significant combination of adenoma/carcinoma should be reported in the labeling. Phenobarbital is labeled as being carcinogenic in mice.

Rat Carcinogenicity The high-dose of 60 mg/kg in rats should be considered to be higher than the MTD. The drug drastically reduced the weights of the treated rats, causing the mid- and high-dose groups to weigh much less than the desired 5-10% below the control group. The 24% & 29% reduction in bodyweight in the high-dose male and female groups is likely to have caused these animals to live longer and have fewer tumors than controls. In fact, the high-dose males did live longer than controls. Although it is usually the case that a dose higher than the MTD leads to increased death, in this case it seems to have led to decreased death, at least in HD males.

The types of tumors found in these rats are consistent with the types expected under conditions of liver enzyme induction and over-stimulated thyroid function. The sponsor has conducted studies, upon our recommendation, to demonstrate exaggerated enzyme and hormonal activity. The expected changes in enzyme activity and hormonal plasma concentration occurred, albeit

weakly. However, it is not clear that the statistical increase in hepatocellular adenoma in female rats of this study was caused by the drug or more directly related to enzyme induction. Adenoma and carcinoma occur in untreated Sprague-Dawley female rats spontaneously at rates of 5% and 1.4%, respectively. Earlier in this review, I cited a report from Ciba-Geigy (McMartin et al., 1992). They used control groups of 60-70 rats (same strain as that used by Organon) in 9 two-year studies. The range for hepatocellular adenoma within the 9 control groups went up to 21.7% in females and was slightly lower in males. Hepatocellular carcinoma ranged up to 1.4%, per control group. In this study, the rates were 10% (5/50) for adenoma and 2% (1/50) for carcinoma in high-dose females. However, the fact that all 12 rats with hepatocellular adenoma were from the mid- and high-dose groups does suggest that there may be a drug relationship. The sponsor reported that these rates were within the range of their historical controls, although those data were not submitted. We have requested this information from the sponsor and they are preparing a submission as of the date of this review.

There were no control groups in the Ciba-Geigy data in which hepatocellular adenoma did not occur. In the current rat study, most of the tumor types that were found had a zero incidence in the control group, including adenoma in the liver. This is probably an unusual outcome. Therefore, even though the incidence of hepatocellular adenoma in the treated groups was not above the range of historical controls, the control group was lower than the range of historical controls. This accentuates the importance of tumors found in the treated groups. Finally, because the liver adenoma in female rats were statistically significantly increased in treated female rats, this fact should be reported in labeling.

Increased thyroid follicular tumor incidence is a known effect of drug-induced hepatic induction in the rat (McClain et al., Studies on the mode of action for thyroid gland tumor promotion in rats by phenobarbital. *Toxicol Appl Pharmacol*, 94:254-65, 1988). The accepted mechanism involves an increase in thyroxine (T_4) turnover, which leads to disinhibition of thyroid stimulating hormone (TSH) secretion. The resulting thyrotropic action of TSH may then lead to follicular tumorigenesis. This mechanism appears to be a possible basis for the dose-related increase in thyroid tumors observed in male rats dosed with ORG 3770. The work of McClain et al. showed that an increase in tumor promotion by phenobarbital could be blocked simply by administering thyroxine to the rats. This presumably reduced the excessive production of TSH through feedback on the pituitary thereby reducing stimulation of the thyroid. There is enough evidence for increased TSH release in rats treated with ORG 3770

to expect that the tumors found in the thyroid were not directly caused by the drug, but through a hormonal imbalance. However, it is known with phenobarbital that bile flow, the hepatic binding of thyroxine, the bile to plasma concentration ratio, and the biliary clearance of thyroxine are increased in rats. We don't know if ORG 3770 affects any of these parameters. Perhaps, even though both drugs are enzyme inducers, each may induce in a mutually exclusive manner.

The reduced weight gain in conjunction with increased food consumption in treated rats is evidence of a high metabolic rate, probably caused by excessive T_3 and T_4 secretion. This metabolic phenomenon probably did not occur in the 12-month dog study. Findings included increased liver weights in the higher dose groups, but not increased thyroid weights. Although the body weights of the higher-dose dogs were less than controls, there was no increase in food consumption among treated dogs.

Finally, there is no proof that thyroid tumors do not develop in humans as the result of a liver-enzyme-inducing drug. Therefore, the tumors must still be reported in the package insert mentioning the likely mechanism of excessive TSH.

RECOMMENDATIONS

1. The NDA is approvable.
2. The sponsor's proposed labeling is found below with recommended additions appearing under shade and deletions under strike-out. These recommendations may be subject to change after the sponsor submits further information about dose-range-finding studies and historical controls for carcinogenicity studies.

CLINICAL PHARMACOLOGY

Pharmacodynamics

The antidepressant action of mirtazapine is presumed to be linked to potentiation of noradrenergic and serotonergic activity resulting from blockade of α_2 and 5-HT₂ receptors by its (+) enantiomer. Blockade of 5-HT₂ receptors by its (-) enantiomer may also contribute to its antidepressant action. Both enantiomers block central histamine (H₁) receptors. Mirtazapine and its (+) enantiomer have been shown to increase noradrenergic neurotransmission in animal studies. ~~REMERON™ is a centrally active presynaptic α_2 -adrenergic antagonist which has been shown in animal studies to increase noradrenergic neurotransmission. ORG 3770 modulates central serotonin function via an interaction with 5-HT₂ and 5-HT₁ receptors, which may serve to explain its~~

~~antidepressant effectiveness. Both enantiomers of mirtazapine are presumed to contribute to the antidepressant activity, the (+) enantiomer by blocking α_2 and 5-HT₂ receptors, and the (-) enantiomer by blocking 5-HT₂ receptors.~~

~~REMERON™ is also a centrally active histamine (H₁) antagonist. This interaction may explain the initial sedative effects seen in patients REMERON™. REMERON™ possesses anxiolytic properties which may be of benefit in the treatment of anxiety symptoms which are often associated with depression.~~

~~REMERON™ lacks the basic side chain believed to be responsible for the anticholinergic side effects of the traditional tricyclic antidepressants. In clinical studies, REMERON™ displayed fewer anticholinergic side-effects than tricyclic antidepressants to which it was compared and, in particular, REMERON™ did not produce clinically relevant effects on the cardiovascular system at therapeutic doses. When administered in the evening, REMERON™ improves sleep by shortening the time to onset, reducing the number of nighttime awakenings, reducing the time spent awake, and increasing the latency to Rapid Eye Movement (REM) sleep. These clinical observations confirm earlier findings in EEG studies in animals.~~

In healthy normal volunteers, a single dose of REMERON™ (15mg) had moderate effects on subjective and objective psychometric tests designed to detect decreases in cognition, memory, attention, psychomotor performance and muscle tone. The effects of REMERON™ and diazepam appeared to be additive.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis: Carcinogenicity studies were conducted in mice (18 months) and rats (24 months) given mirtazapine in the diet at ~~2, 20, and 200 mg/kg/day doses up to 22 times (mice) and 2, 20 and 60 mg/kg/day 13 times (rats) the maximum recommended human dose on a mg/m² basis. The maximum doses in these studies were approximately 300 (mouse) and 90 (rat) times the maximum daily dose recommended for human use on a mg/kg basis.~~

~~In mice, there were increased ultrastructural changes in hepatocytes which were consistent with enzyme induction and thus a non-genotoxic response. In rats, there was an increased incidence of hepatocellular adenoma in female rats and of hepatocellular adenoma/carcinoma in male mice. There was an increased incidence of thyroid follicular cell adenoma/cystadenoma/carcinoma and carcinoma in high-dose males as~~

~~compared to control animals male rats. These results were These effects are presumed to be due to liver enzyme induction, increased metabolism of thyroid hormones, increased TSH levels and chronic stimulation of the thyroid gland and are not likely to be genotoxic responses. The higher incidence of thyroid follicular cell neoplasms is known to occur in rats when treated with enzyme inducing compounds, and is considered to be a species specific, non-genotoxic response associated with long-term treatment with hepatic enzyme inducers. The relevance of these findings to humans is unknown.~~

~~Mutagenesis: ORG 3770 produced no genotoxic effects in the following four in-vitro mammalian cell assays (sister chromatid exchange test, unscheduled DNA synthesis assay, gene mutation in Chinese hamster V79 cells, the in vivo rat micronucleus test) and one in-vivo bacterial mutation assay (Ames test). sister chromatid exchange test, unscheduled DNA synthesis assay, gene mutation in Chinese hamsters and a micronucleus test in rats.~~

~~Impairment of Fertility: Doses of mirtazapine administered to rats, at approximately 150 times the highest recommended human daily dose on a mg/kg basis, resulted in the increased neonatal mortality and lower body weight. However, estrous cycle patterns, mating and pregnancy performance, pre and post-implantation loss and the physical and behavioral development of offspring were not adversely affected. In a fertility study in rats, mirtazapine was given at doses up to 22 times the maximum recommended human dose (MRHD) on a mg/m² basis. Mating and conception were not affected by the drug, but estrous cycling was disrupted at doses that were 3 or more times the MRHD.~~

Pregnancy

Teratogenic Effects - Pregnancy Category B C: Reproduction studies in pregnant rats and rabbits at doses up to approximately 150 and 60 22 and 17 times the maximum daily recommended human dose (MRHD) on a mg/kgm² basis, respectively, have revealed no evidence of teratogenic effects. However, in rats, there was an increase in pre- and post-implantation losses in dams treated with mirtazapine. There was an increase in pup deaths during the first 3 days of lactation and a decrease in pup birth weights. The cause of these deaths is not known. These effects occurred at doses that were 22 times the MRHD, but not at 3 times the MRHD, on a mg/m² basis. There are no adequate and well controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers

REMERON was found to be excreted in small amounts in the milk of lactating rats. As with other antidepressants, care should be exercised when REMERON is administered to nursing women.



STEVEN SPARENBORG, Ph.D.

cc: NDA 20-415
HFD-120
HFD-120/GFitzgerald
/SSparenborg

August 14, 1995

REVIEW AND EVALUATION OF CARCINOGENICITY STUDIES

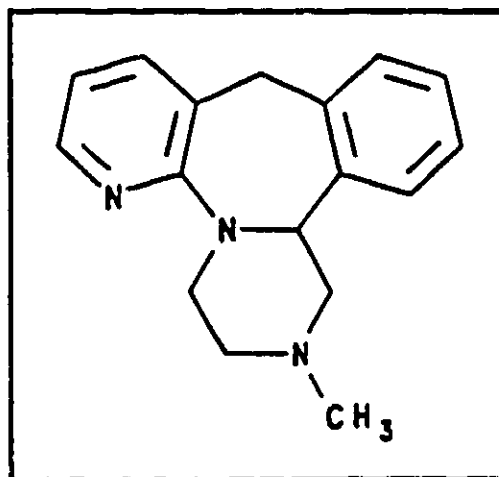
NDA 20-415

Reviewer: Steven Sparenborg, Ph.D.

Sponsor: Organon, Inc.
West Orange, NJ

Drug: REMERON® (6-azamianserin, mirtazapine, ORG 3770)

Chemical name: 1, 2, 3, 4, 10, 14b-hexahydro-2-methylpyrazino [2, 1-2] pyrido [2,3-c][2]benzazepine



Category: α_2 , 5-HT₂, 5-HT₃ antagonist

Indication: depression

Background: This drug was negative in the Ames, gene mutation in Chinese hamster V79 cells, *in vivo* rat micronucleus, unscheduled DNA synthesis in HeLa S3 cells, and sister chromatid exchange tests.

The sponsor did not submit dose-range-finding studies with this NDA.

"An 18 month carcinogenicity feeding study in mice with ORG 3770"

CD-1 mice (50/sex/dose) were given the test drug in the diet at doses of 0, 2, 20, and 200 mg/kg.

1. The FDA statistician, Dr. Daphne Lin, used the Cox test and the generalized Wilcoxon test to analyze survival. There were no significant effects. The data were analyzed by gender and by two time periods, 0-50 weeks and 51-78 weeks. The figure below uses 3 six-month time periods.

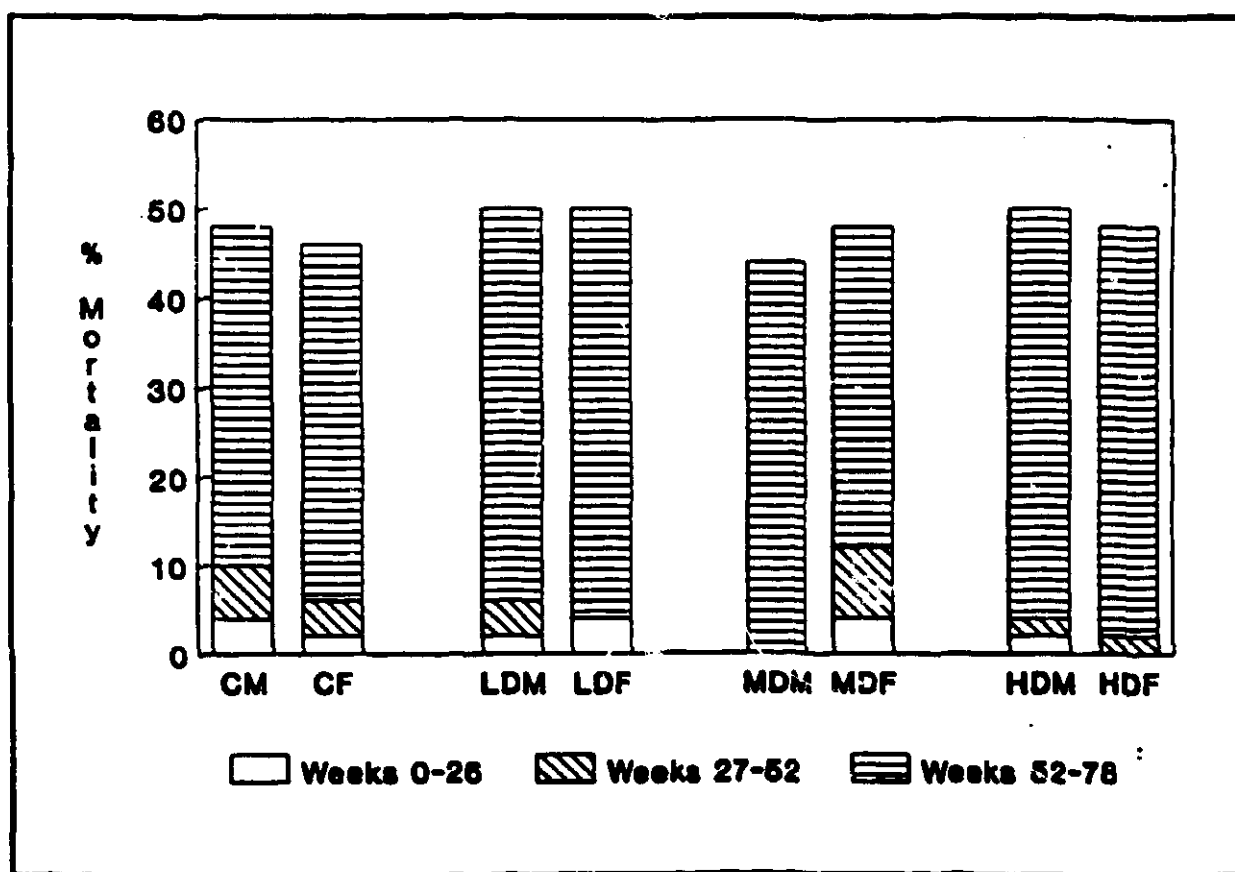


Figure 2 - Premature Mortality

The causes of death were unrelated to the test drug.

2. Weight effects were very slight. Male high-dose mice weighed 6% less than controls and female high-dose mice weighed 4% less. Mid- and high-dose males and females ate more food than controls ($p < .01$; see the tables on the following pages).

Male Mice Body

— Day 1 - 0 days
— Day 15 - 15 days
— Day 30 - 30 days
— Day 45 - 45 days



Male Mice Food

— Day 1 - 0 days
— Day 15 - 15 days
— Day 30 - 30 days
— Day 45 - 45 days



Female Mice Body

— Day 1 - 0 days
— Day 15 - 15 days
— Day 30 - 30 days
— Day 45 - 45 days



Female Mice Food

— Day 1 - 0 days
— Day 15 - 15 days
— Day 30 - 30 days
— Day 45 - 45 days



3.

Table 1 - Neoplastic Findings *Mouse*

		C	LD	MD	HD
Hepatic adenoma	♂	3	3	6	10 ^a
	♀	1	2	1	0
Hepatic carcinoma	♂	4	2	5	8
	♀	0	0	0	1
Hepatic hemangioma/sarcoma	♂	1	3	1	0
	♀	3	2	1	0
Lung carcinoma/adenoma	♂	4	3	1	2
	♀	3	0	0	4
Malignant lymphoma	♂	1	0	1	1
	♀	3	1	2	2
Granulocytic leukemia	♀	0	0	0	1
Histiocytic sarcoma	♂	0	0	0	1
	♀	1	0	1	0
Testicular interstitial cell tumor	♂	0	1	1	0
Mammary carcinoma	♀	0	0	1	0
Ovarian cystadenoma	♀	0	1	1	0
Uterine sarcoma/leiomyoma	♀	2	1	1	1
Endometrial stromal polyps	♀	1	0	2	3
Other	♂	1	1	3	0
	♀	1	2	0	2

^ap < .05 vs. control (Fisher)

Gross necropsy indicated an increase in drug-treated males with liver masses or nodules (10, 10, 22 and 28% in C, LD, MD and HD, respectively). This finding was confirmed histopathologically by an increased incidence of hepatic adenoma and carcinoma in HDM (table 2). However, the FDA statistical reviewer used the methods of Peto and

the exact permutation trend test to analyze the tumor data. After correcting for multiple testing, no tumor types were found to be statistically significant.

The sponsor reported a separate study in which male mice were given 200 mg/kg in the diet for 4 or 28 days in which ORG 3770 induced activities of cytochrome P₄₅₀ (41-58%), aminopyrine-N-demethylase (70-86%), aniline hydroxylase (32-67%), 7-ECOD (132-193%). The activity of p-Nitrophenol-glucuronyl-transferase was not affected. Examination of animals not bearing hepatic tumors did indicate an increase in hepatic vacuolation (10, 12, 17 and 13/50 in CM, LDM, MDM and HDM), possibly due to induction. Comparison of electron photomicrographs of livers from 3 CM and 15 HDM revealed modestly increased smooth endoplasmic reticulum in the drug-treated animals, which is indicative of enzyme induction. According to the sponsor, there were no other significant changes in the incidence of neoplasms.

The most frequent nonneoplastic findings included amyloidosis of the heart, spleen, adrenals, liver and GI tract, chronic pneumonia, mesenteric congestion and lymphoid hyperplasia, chronic nephropathy, testicular degeneration and uterine endometrial hyperplasia. None of these appeared to be affected by ORG 3770 treatment, but instead were consistent with age-related findings in this species.

"A 24 month feeding study in rats with ORG 3770"

Sprague-Dawley rats (50/sex/dose) were given the drug in the diet at doses of 0, 2, 20 and 60 mg/kg.

1. The Cox and Wilcoxon tests were used to analyze mortality. A significant effect ($p < .01$) was found in male rats. As can be seen in the figure below, it is due to increased survival in high-dose males. There was no effect of the drug on survival in female rats.

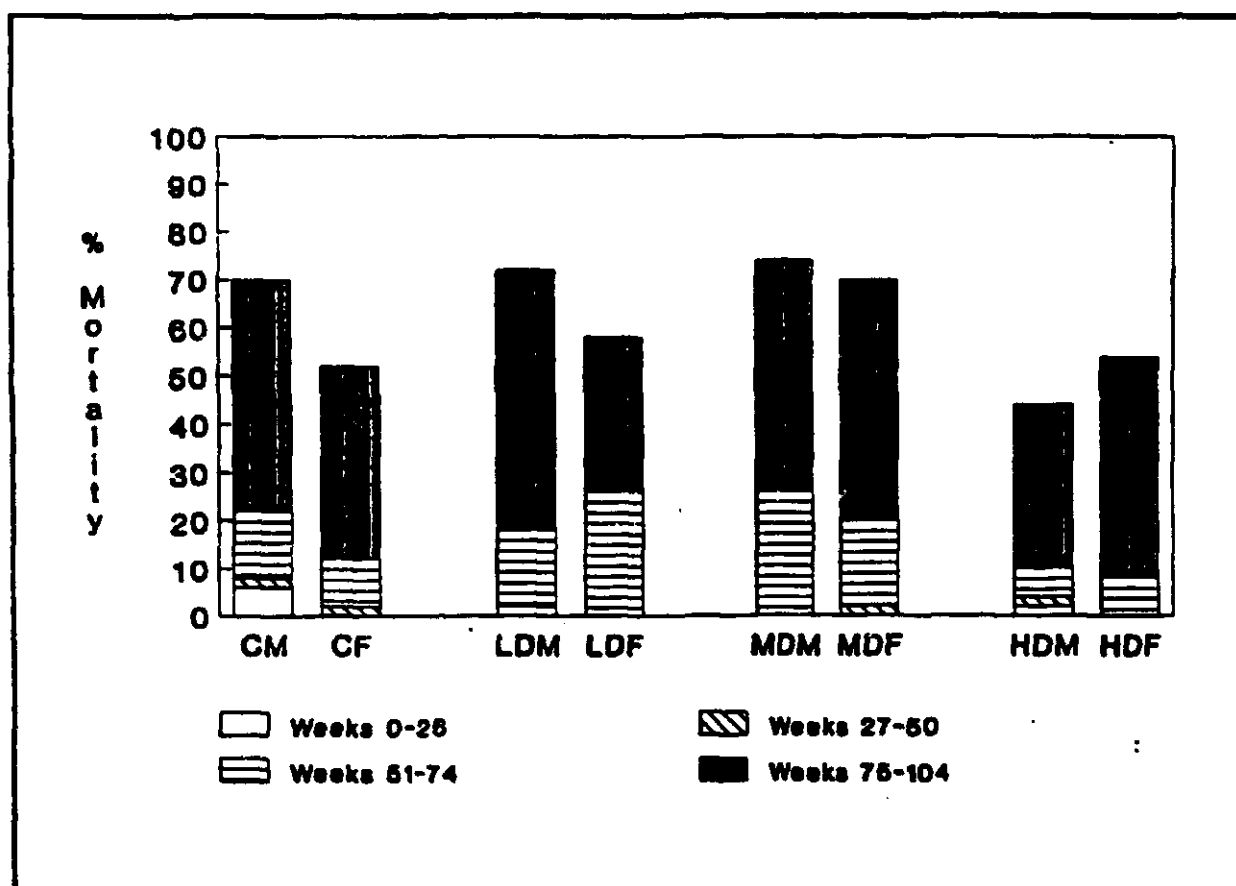
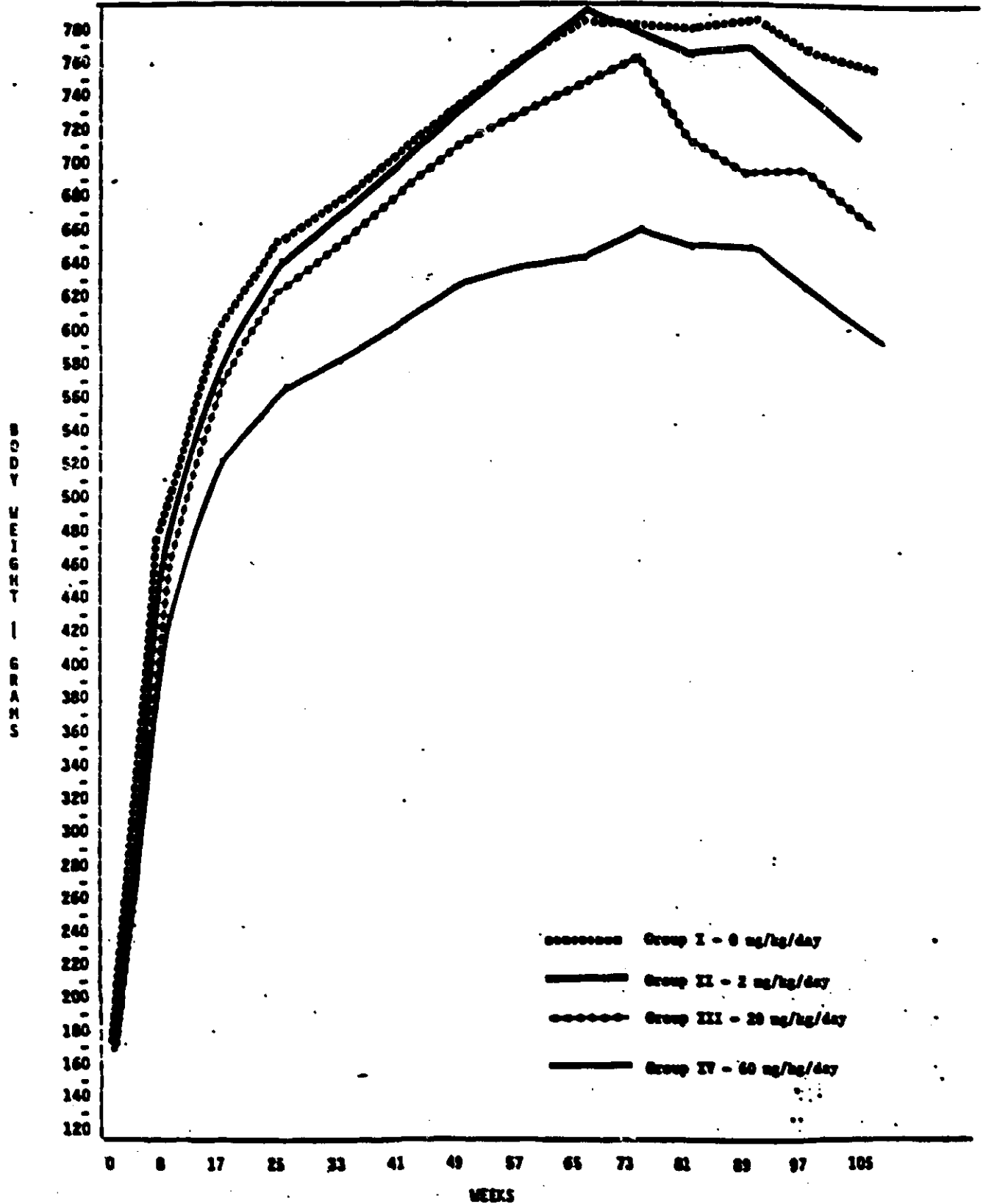


Figure 3 - Premature Mortality

2. Food consumption was increased in all treated groups throughout the study. The mid- and high-dose groups ate significantly more ($p < .01$) than controls in most monthly samples, yet they did not gain as much weight as did controls. At the end of the study, mean body weights (percent of control) in the male L, M and H groups were 94%, 87% and 76%. Female terminal mean body weights were 94%, 86% and 71% of controls, respectively. See the graphs of bodyweight and food consumption below.

Graphic Representation of Mean Body Weight Data - Males



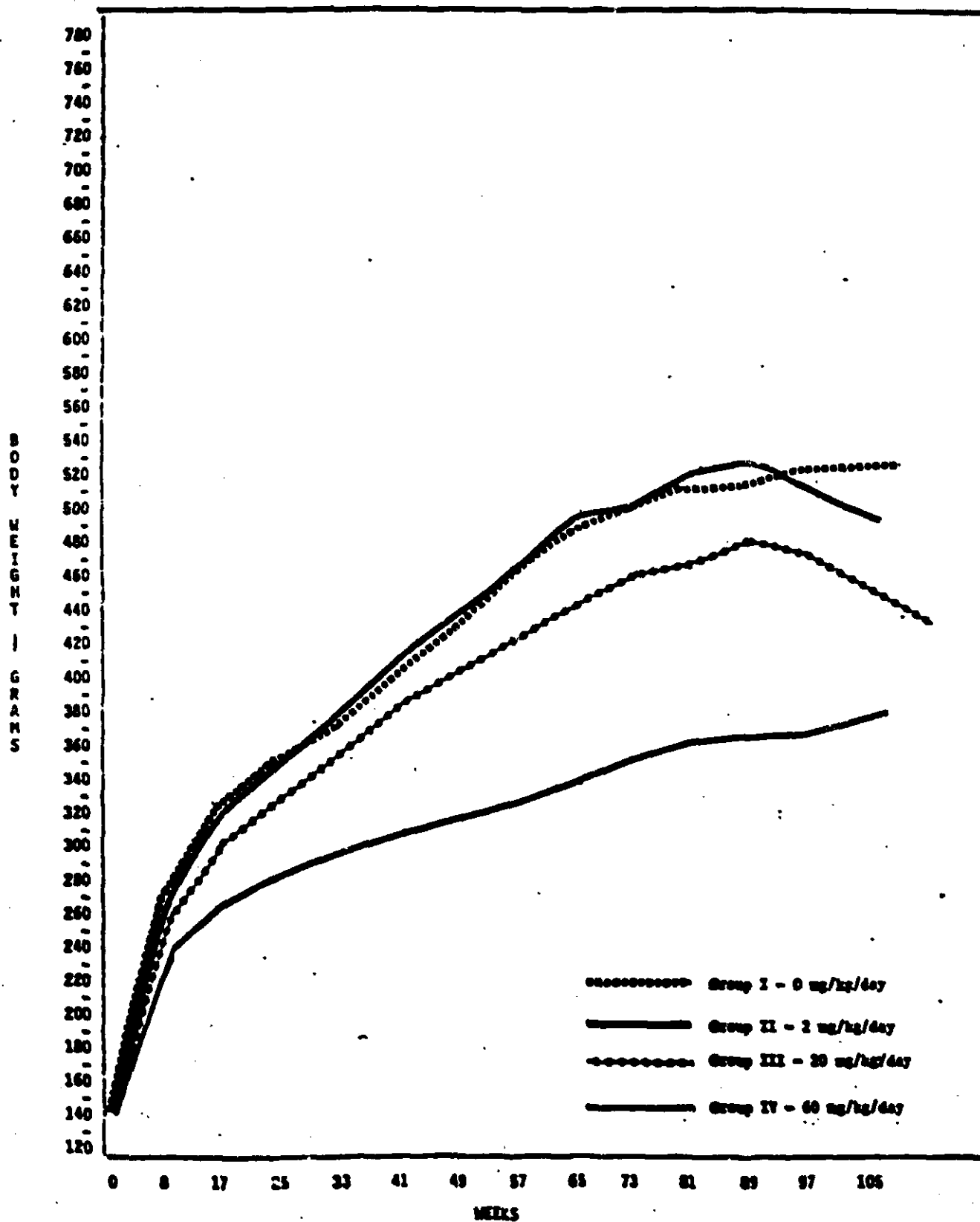


CONFIDENTIAL

F 2-1
Figure 2
A Twenty-Four Month Feeding Study
in Rats with OHS 3770

85-2938

Graphic Representation of Mean Body Weight Data - Females



0022

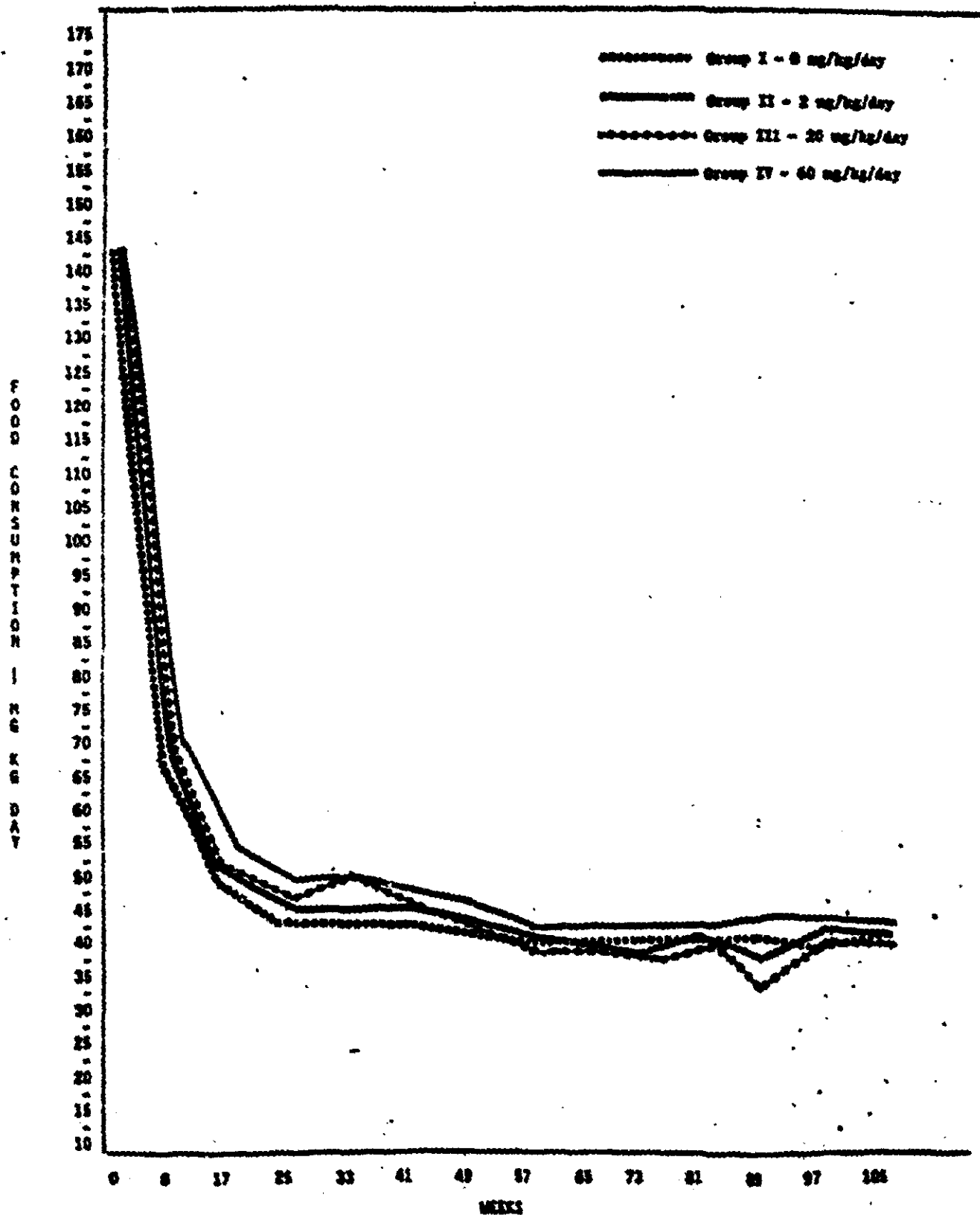


CONFIDENTIAL

F 3-1
Figure 3
A Twenty-Four Month Feeding Study
in Rats with OHS 3770

00-2331

Graphic Representation of Food Consumption Data -- Males



FORM 2470 10/73

0023



CONFIDENTIAL

F 4-1
Figure 4
A Twenty-Four Month Feeding Study
in Rats with GRS 3770

65-2938

Graphic Representation of Food Consumption Data - Females

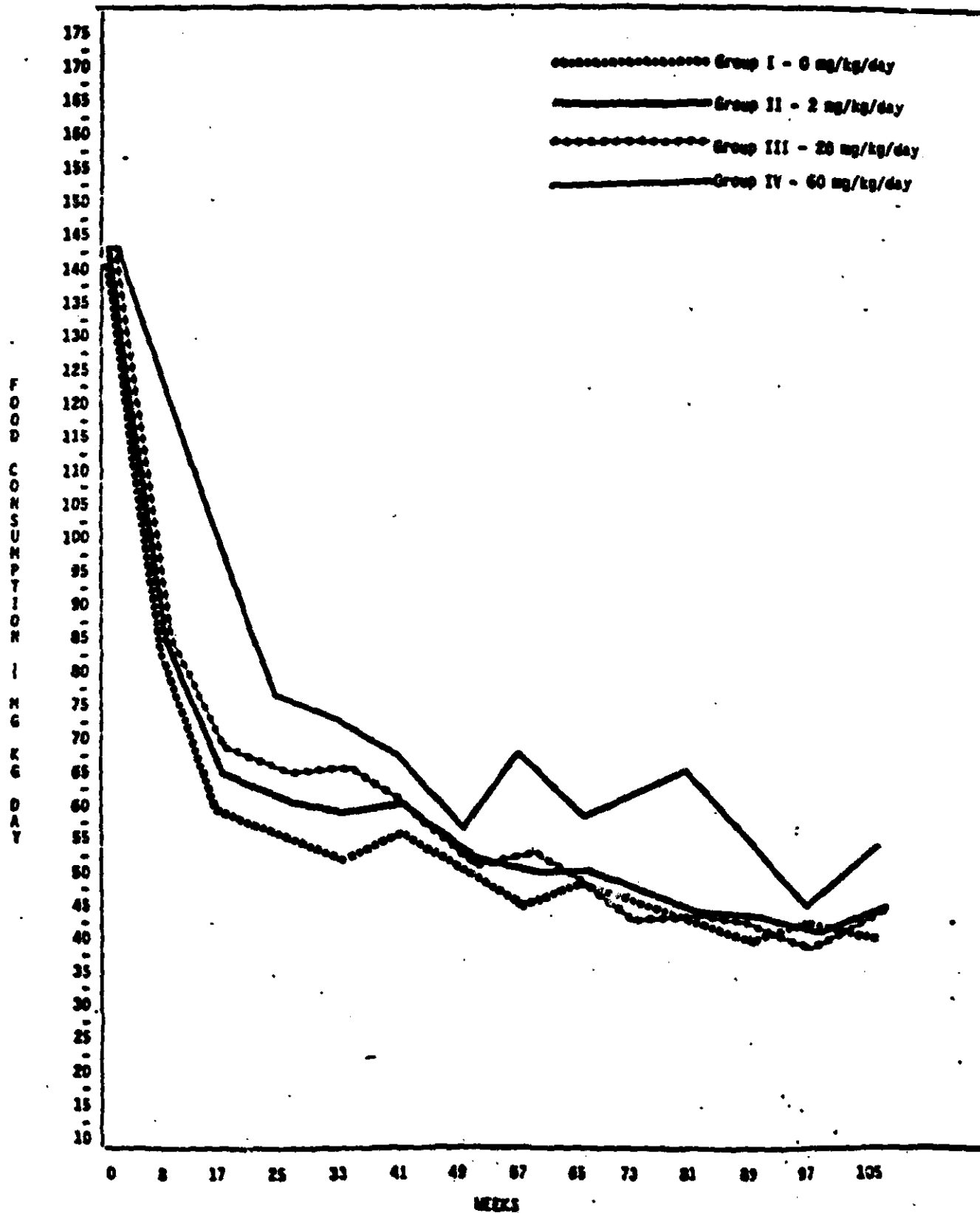


Table 3 - Neoplastic Findings

		<u>C</u>	<u>LD</u>	<u>MD</u>	<u>HD</u>
Hepatocellular adenoma	♂	0	0	0	3
	♀	0	0	4	5 ^a
Hepatocellular carcinoma	♂	1	1	1	3
	♀	1	0	0	1
Thyroid follicular adenoma	♂	1	4	5	9 ^a
	♀	1	1	1	1
Thyroid follicular carcinoma	♂	0	1	1	3
	♀	0	0	1	0
Thyroid C-cell adenoma	♂	5	3	7	7
	♀	2	7	2	3
Thyroid C-cell carcinoma	♂	0	0	1	0
	♀	0	1	1	0
Testicular interstitial cell tumor	♂	0	2	0	3
Uterine endometrial sarcoma	♀	0	0	0	2
Other uterine/ovarian tumors	♀	1	0	0	2
Uterine endometrial polyps	♀	1	0	3	4
Mammary fibroadenoma	♀	12	11	13	7
Mammary adenoma	♀	1	2	2	1
Mammary fibroma	♀	4	0	0	0
Mammary carcinoma	♂	0	2	0	0
	♀	14	13	13	19
Mammary fibrosarcoma	♂	1	0	0	1
	♀	1	0	1	0
Mammary lipoma	♂	0	0	0	0
	♀	1	0	1	0
Adrenal adenoma	♂	0	1	1	0
	♀	3	2	1	3
Adrenal carcinoma	♂	1	0	0	0
	♀	0	0	0	2

Table 3 (continued)

Pheochromocytoma	♂	4	6	7	2
	♀	1	2	0	3
Pancreatic islet cell adenoma	♂	4	1	2	2
	♀	2	1	3	1
Pituitary adenoma	♂	22	24	22	22
	♀	47	43	45	35
Pituitary carcinoma	♂	0	1	0	0
	♀	2	1	1	3
Renal lipoma	♂	0	1	1	0
	♀	0	0	0	1
Brain glioma	♂	0	2	0	2
	♀	0	0	0	1
Skin squamous cell papilloma	♂	4	3	3	2
	♀	2	1	0	1
Skin squamous cell carcinoma	♂	0	0	0	1
	♀	0	0	0	1
Skin fibroma/fibrosarcoma	♂	0	2	0	2
	♀	1	1	4	2
Histiocytic sarcoma	♂	2	2	0	0
	♀	0	0	2	0
Malignant lymphoma	♂	1	0	0	1
	♀	2	0	0	0
Granulocytic leukemia	♂	0	1	0	1
	♀	0	0	0	0
Other	♂	3	3	1	5
	♀	2	2	1	2
# Tumor-bearing animals	♂	34	39	36	37
	♀	47	47	48	48
Total tumor count	♀	70	93	52	87
	♀	104	96	115	113

^ap < .05 (Fisher)

The sponsor reported, as found in the above table, that there was a significant linear trend in hepatocellular adenoma in female rats and thyroid follicular cell adenoma in male rats. The FDA statistician also found these two tumor types to be significantly increased. Using the age-adjusted method, a linear trend was found in the incidence of hepatocellular adenoma in females, $p = 0.008$. Using the age unadjusted method, a linear trend was found in the incidence of thyroid follicular cell adenoma, $p = 0.0045$. The age-unadjusted method was used because not all thyroids were available for examination (48, 49, 50 and 46 rats from the male C, L, M and H groups). Paired comparisons of the control and high-dose groups were not significant for either tumor type.

The sponsor reported that the rate of hepatocellular adenoma was within the range of their historical controls. In an independent collection of 585 Crl:CD rats tested between 1984 and 1991, the average rate of hepatocellular adenoma was 5% for males and females (McMartin, et al., *Toxicologic Pathology*, 1992, 20(2), 212-225). Another independent source also rates these tumors at 5% in controls of this strain (Greaves and Faccini, *Rat Histopathology*, 2nd Edition, Elsevier, Amsterdam, 1992).

The historical control rate for thyroid follicular cell adenoma, however, is well below the rate found in this study. HFD-120 recommended, in 1991, that the sponsor conduct studies to demonstrate that the liver and thyroid tumors found in rats were due to enzyme induction and hormonal effects, as the sponsor claimed. Subsequently, they treated male rats for 14 days with 60 mg/kg/day in the diet and found that microsomal protein increased to 135% of controls on Day 15 when measured as total protein. The activity of the following substances was significantly ($p < .01$) increased in treated rats on Days 5 and 15: cytochrome P450, 180% of controls; 7-EROD, 600% of controls. P-nitrophenol UDPGT was increased on Days 5 and 15 to 170% of controls, ($p < .05$). T_3 and TSH levels in plasma were not affected, but T_4 was 80% of control values ($p < .05$). In a 90-day study using the same dose level, T_4 plasma concentration was not consistently lower in treated rats. TSH was increased in the drug-treated rats by 20-40% on Days 14 and 28, but not Day 92 ($p < .05$). Other rats treated with phenobarbital in this study had reduced T_3 and T_4 levels and increased TSH concentrations, but not at every sampling time (Days 0, 4, 14, 28, 92).

SUMMARY

MORTALITY

- no effect on mortality in mice
- linear trend for survival in male rats, indicating that the drug decreased mortality in the high-dose group (percent survival after 24 mos. in controls = 30, in high-dose males = 56)
- no effect on mortality in female rats

BODYWEIGHT

- terminal sacrifice body weights of male mice were 6% lower than controls and females were 4% less than controls, neither group significantly different from the respective control group. With a large number of mice still alive in each group ($n = 26-31$), it could be expected that even these small percentage differences should be significant, but they weren't.
- the increased food consumption by treated mice, compared to controls, probably helped keep bodyweight decreases to a minimum and suggests that general metabolism may have been increased in the high dose group.
- food utilization in drug-treated rats was also poor, especially in females. High-dose females ate 130% as much food as controls, but their body weights were only 71% of controls. Mid-dose females ate 111% as much as controls but weighed only 86% of controls. Male body weights for the L, M and H groups were 94%, 87% and 76% of controls and their food consumption was 104%, 105% and 111% of controls, respectively.

OTHER TOXIC FINDINGS

- differential leucocyte counts were taken in both mice and rats, but no relationship to the drug was found. Gross and histopathological lesions, other than the tumors reported herein as statistically significant, were of the type normally encountered in aged rodents and were not related to drug treatment.

TUMORS SPECIAL STUDIES OF ENZYMES AND HORMONES

- there were no statistically significant tumor types in mice, but there were clear signs of toxicity in the liver. Adenoma (3, 3, 6, 10 in C, L, M, H groups) and carcinoma (4, 2, 5, 8) appeared to be increased in male mice, as were the number of mice with liver

masses or nodules. Male mice had increased activity of liver enzymes, including P450. There was also ultrastructural evidence of induced enzyme activity in the form of modestly increased smooth endoplasmic reticulum in males of the high-dose group.

- like male mice, male rats had an apparent, but not significant, increase in hepatocellular adenoma (0, 0, 0, 3 in C, L, M, H groups). Female rats had a significant increase in hepatocellular adenoma (0, 0, 4, 5; $p = 0.008$, trend test). The sponsor then tested male rats for liver enzyme activity and found increased P450, 7-ethoxyresorufin-O-deethylase, and UDP-glucuronyltransferase activity. The number of rats with these tumors in this study is within the range of historical controls. However, the occurrence of these tumors here was only in the groups treated with higher doses of the drug.
- male rats had a statistically significant increase in thyroid follicular cell adenoma/cystadenoma (1, 4, 5, 9 in C, L, M, H groups; $p = 0.0045$, trend test). T_4 levels in plasma were found, in a subsequent study, to be lower in rats treated with the high-dose used in the carcinogenicity study, than in controls, but TSH levels were not affected by the drug. In yet another study, TSH levels were found to be elevated during the first month of treatment, but not after 3 months. T_4 levels fluctuated above and below the levels of controls.

MUTAGENICITY

- this drug was negative in the Ames, SCE, *in vivo* rat micronucleus, unscheduled DNA synthesis, and Chinese hamster V79 mutation assays.

EVALUATION

The slight weight reductions in high-dose mice suggest that the dose of 200 mg/kg was close to the MTD. The increased food consumption stimulated by the drug probably prevented greater weight disparities in these mice. This drug did not increase mortality or cause any form of pathology except to stimulate liver activity. Therefore, the high-dose of 200 mg/kg should be accepted as the MTD for mice. Dose-range-finding studies were not submitted with this NDA.

The high-dose of 60 mg/kg in rats should be considered to be higher than the MTD. The drug drastically reduced the weights of the treated rats, causing the mid- and high-dose groups to weigh much less than the desired 5-10% below the control group. The 24% & 29% reduction in bodyweight in the high-dose male and female groups is likely to have caused these animals to live longer and have fewer tumors than controls. In fact, the high-dose males did live longer than controls. Although it is usually the case that a dose higher than the MTD leads to increased death, in this case it seems to have led to decreased death, at least in HD males.

The types of tumors found in these mice and rats are consistent with the types expected under conditions of liver enzyme induction and over-stimulated thyroid

function. Hepatic microsomal induction is an accepted non-genotoxic mechanism by which certain tumor types may be increased in animals. Thus, hepatic tumors may be induced in mice by known inducing agents (e.g. phenobarbital). Hepatocellular adenoma in untreated Sprague-Dawley rats occur spontaneously at a rate of 5%. This tumor type had a rate in this study of 4.5% in females and 1.5% in males. However, the fact that all 12 rats with hepatocellular adenoma were from the mid- and high-dose groups does suggest that there may be a drug relationship. The sponsor reported that these rates were within the range of their historical controls.

Increased thyroid follicular tumor incidence is a known effect of drug-induced hepatic induction in the rat (McClain et al., Studies on the mode of action for thyroid gland tumor promotion in rats by phenobarbital. *Toxicol Appl Pharmacol*, 94:254-65, 1988). The accepted mechanism involves an increase in thyroxine (T_4) turnover, which leads to disinhibition of thyroid stimulating hormone (TSH) secretion. The resulting thyrotropic action of TSH may then lead to follicular tumorigenesis. This mechanism appears to be a possible basis for the dose-related increase in thyroid tumors observed in male rats dosed with ORG 3770.

The sponsor has conducted studies, upon our recommendation, to demonstrate exaggerated enzyme and hormonal activity. The expected changes in enzyme activity and hormonal plasma concentration occurred, albeit weakly, in mice and rats. Therefore, the hepatocellular adenoma in mice should not be considered to be genotoxic events because 1) their occurrence was not statistically significant and 2) any increase in tumors of this type can be attributed to the enzymatic induction which occurs in mice. The hepatocellular adenoma in female rats were statistically significant but were within the range of historical controls, and therefore, need not be considered to be drug-induced. The thyroid follicular adenoma in rats probably occurred as a correlate of the induction of liver enzymes, not as a direct effect of the drug. This tumor type should be reported in labeling along with an explanation of the probable mechanism of action.

RECOMMENDATIONS

1. These studies should be accepted.
2. The sponsor's proposed labeling is found below with recommended changes.

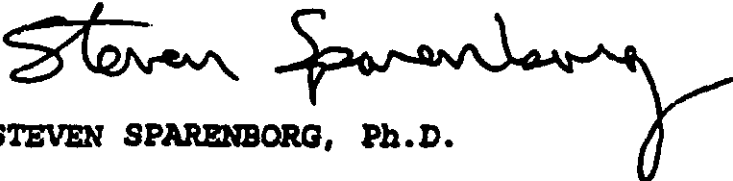
Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis: Carcinogenicity studies were conducted in mice (18 months) and rats (24 months) given mirtazapine in the diet at 2, 20, and 200 mg/kg/day [REDACTED] (mice) and 2, 20 and 60 mg/kg/day [REDACTED] (rats) [REDACTED]. The maximum doses in these studies were approximately 200 (mouse) and 90 (rat) times the maximum daily dose recommended for human use on a

mg/kg basis.

In mice, there were increased ultrastructural changes in hepatocytes which were consistent with enzyme induction and thus a non-genotoxic response. In rats, there was an increased incidence of thyroid follicular cell adenoma/cystadenoma and carcinoma in high dose males as compared to control animals. These results were due to liver enzyme induction, increased metabolism of thyroid hormones, increased TSH levels and chronic stimulation of the thyroid gland. The higher incidence of thyroid follicular cell neoplasms is known to occur in rats when treated with enzyme inducing compounds, and is considered to be a species-specific, non-genotoxic response associated with long-term treatment with hepatic enzyme inducers.

Mutagenesis: Mirtazapine produced no genotoxic effects in the following four *in-vitro* assays and one *in-vivo* bacterial mutation assay. The assays included sister chromatid exchange test, unscheduled DNA synthesis assay, gene mutation in Chinese hamsters and a micronucleus test in rats.


STEVEN SPARENBORG, Ph.D.

cc: NDA 20-415
HFD-120
HFD-120/GFitzgerald 9/7 2/10/10
/SSparenborg

Barry N. Rosloff
11/21/95

**Pharmacologist Review of NDA 20-415
Update on Review of Carcinogenicity Studies**

SPONSOR: Organon, Inc.
West Orange, NJ

DRUG: Remeron (6-azamianserin, mirtazapine, ORG 3770)

CATEGORY: antidepressant

PREVIOUS PHARMACOLOGIST REVIEW: NDA review of 9/20/95 (Dr. Sparenborg).

INTRODUCTION:

Several questions regarding the results and interpretation of the mouse and rat carcinogenicity studies were raised in the above review and at a meeting of the CAC executive committee held 8/22/95. In general these questions concerned (1) the adequacy of the doses in the mouse study, (2) which tumors can be considered to have been increased in incidence by drug treatment, and (3) the evidence for and plausibility of the sponsor's proposed mechanisms for the drug-induced liver and thyroid tumors. In response to our request for more information, the sponsor's submission of 9/28/95 contains a 9 week mouse rangefinding study, historical control tumor data (from the lab performing the studies), and a study of the effect of the drug on hepatic enzyme induction and thyroid function in rats. (Additional enzyme induction and thyroid studies have been previously submitted and reviewed). The following will discuss the above questions in light of the sponsor's submission of 9/28/95 as well as previous data submitted to this NDA.

(1) ADEQUACY OF DOSES IN MOUSE STUDY

The doses used in this study were 2, 20, and 200 mg/kg/day given in diet. Aside from an increase in hepatocytic hypertrophy and hepatic tumors in HD males, there were no clearly drug-related effects seen in this study. (As mentioned in the previous review, slight [$< 5\%$ below controls] decreases in bodyweight were seen in HD M. However, this was not seen consistently during the study, and was only statistically significant at a few time points. In the 9 week rangefinding study submitted 9/28/95, no effects on bodyweight were seen up to the highest dose tested, 480 mg/kg. The previous review also noted a slight increase in food consumption in HD M; however this was based on food consumption expressed as grams of food consumed per kg of bodyweight and thus probably just reflects the slightly lower bodyweights in this group; a spot check of the data on amount of food consumed per animal shows no drug effect. The sponsor also claims that EM exams done in this study showed an increased amount of hepatic SER in HD M; however, the numbers of animals examined are too small [3 controls and 12 treated] and the results too variable to conclude an effect [see attached table] [and furthermore, although not explicitly stated, it appears that all 3 controls but only 3 of the 12 treated mice had been previously examined using a different method of sampling and were found to have low amounts of SER, resulting in a possible bias in the subsequent examination]. [On the other hand, in a separate study in mice, males given 200 mg/kg/day in diet showed an increase in biochemical parameters of enzyme induction, indicating some effect is demonstrable at this dose, although not one which is useful for determining an MTD]).

It is thus concluded that an MTD was not reached in the mouse study; furthermore it is not possible to estimate how close the HD (200 mg/kg) was to an MTD. The 9 week rangefinding study showed no effects (signs, deaths, food consumption, bodyweights, lab tests, gross pathology) up to 480 mg/kg. It is also noted that in view of the above, the LD (2 mg/kg) and MD (20 mg/kg) used were extremely low.

(At the full CAC meeting on 11/16/95, the sponsor showed data indicating that the mouse/human plasma AUC ratio for parent drug was about 1 [at a mouse dose of 200 mg/kg in diet]; these data have not been submitted for review, but at any rate the relative amounts of metabolites must also be considered for this drug since it is extensively metabolized).

(In contrast, the doses in the rat carcinogenicity study reached, and probably even exceeded, the MTD, based on decreased bodyweight gain. [This decrease was probably not secondary to decreased palatability since despite decreased weight gain in both sexes at both MD and HD, food consumption was decreased (slightly) only in HD M, and this occurred only during the latter part of the study whereas weight gain was decreased throughout.]. [The sponsor concluded that food consumption was

increased at MD and HD; however this was based on grams consumed per kg bodyweight; a spot check of the data for grams consumed per animal showed a slight decrease in HD M as mentioned above)).

Distribution of SER* Scores in Mice		
Score	Control M	HD M
40-60	3	4
60-80		5
80-100		0
100-120		2
120-140		3
140-160		1

(From CA study)

~~n:resleff/messersch~~

* Smooth endoplasmic reticulum

(2) TUMOR DATA

A table showing the incidence values of the tumors being considered here is attached. The table shows the % incidence of the tumors found in the Remeron studies as well as the historical control values as provided by the sponsor. (Note that this table does not indicate results of statistical tests. The following discussions of likely drug effects focus primarily on comparison of incidence values with concurrent and historical controls, and on biological plausibility. Not all of the effects which I consider to likely be drug related were statistically significant. [Also, I have some questions about the statistical approaches used, e.g. the alpha levels used for the various tests seem arbitrary and inconsistently applied, and pairwise comparisons were only done if the linear trend was significant (and even then, the pairwise comparison was limited to control vs HD). The results of the statistical tests can be found in the Statistical Reviews of 6/30/95 and 9/6/95.]).

(A) Male Mouse Liver

Hepatocellular adenomas and carcinomas (either alone or combined) were increased at HD. The incidences at HD were above the sponsor's historical control ranges. (Centrilobular hepatocyte hypertrophy was also increased in HD M: 10/50 vs 0/50 controls).

(B) Female Rat Liver

Hepatocellular adenomas were increased at MD and HD. The incidences were above the historical control range. There was no increase in carcinomas. An equivocal slight increase in eosinophilic foci (a putative pre-neoplastic lesion) was seen at MD and HD, and an equivocal slight increase in hepatocellular hypertrophy was seen at HD (10%, vs 2% in control).

(C) Male Rat Liver

It is difficult to conclude there is a drug effect on either hepatocellular adenomas or carcinomas alone due to the small numbers (remember that the table shows % incidence; sample sizes were ~ 50 and thus the numbers of animals affected are about ½ the numbers in the table). However, the incidence of animals with either adenoma or carcinoma was possibly increased at HD; the incidence at HD is well above the historical control mean although not above the upper end of the historical control range. The likelihood of the above being drug-related is supported by the increase in eosinophilic foci at HD (and equivocally also at the lower doses.). (Note that the finding of increased eosinophilic foci was not discussed in either the study report summary or in any of the sponsor's summaries of the carcinogenicity results).

(D) Male Rat Thyroid

Follicular adenomas/cystadenomas were increased at HD. The incidence of follicular carcinomas was equivocally increased at HD; the number of affected animals was small, but a drug effect is supported by the fact that the incidence was above the historical control range as well as by the fact that the incidence of adenomas was increased. The incidence of animals with either adenoma/cystadenoma or carcinomas was clearly increased at HD. The incidence of adenoma/cystadenoma and of either adenoma/cystadenoma or carcinoma was equivocally increased at LD and MD; the incidence values were at the upper end of the historical ranges.

(E) Rat Uterine Tumors

The question of a possible drug effect was raised at the CAC executive committee meeting of 8/22/95. As shown in the attached tables, the incidence values were quite low and not unexpected based on the historical control values submitted by the sponsor (and present in the literature). There was no indication of any other effect (e.g. hyperplasia) on the uterus. There were no drug effects on the uterus in the 12 month rat toxicity study (HD = 120 mg/kg/day in diet).

TUMOR INCIDENCES (%)

Mouse Liver (males)				
	C	LD	MD	HD
adenoma	6	6	12	20
carcinoma	8	4	10	16
either	14	10	22	34

HISTORICAL CONT

$\bar{x}$	Range
-----------	-------

10 3-17

7 2-14

Rat Liver (males)				
	C	LD	MD	HD
adenoma	0	0	0	6
carcinoma	2	2	2	6
either	2	2	2	12
(eosinophilic foci)	4	10	16	28
(females)				
adenoma	0	0	8	10
carcinoma	2	0	0	2
either	2	0	8	12
(eosinophilic foci)	6	2	18	14

1 0-3

2 0-9

2.5 0-5.8

Rat Thyroid (males)				
	C	LD	MD	HD
adenoma/ cystadenoma	2	8	10	20
carcinoma	0	2	2	7
either	2	10	12	26

3.2 0-10

1 1-3

*** PATH/TOX SYSTEM OUTPUT ***
A TWENTY-FOUR MONTH FEEDING STUDY
IN RATS WITH ORG 3770
INCIDENCE SUMMARY

PRINTED: 10-MAY-90
PAGE: 9

STUDY NUMBER: 852938

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TABLE INCLUDES:

SEX=ALL; GROUP=ALL; SCREEN=ALL; WEEKS=ALL
DEATH=ALL; FIND=ALL; SUBSET=1

NUMBER OF ANIMALS AFFECTED

ORGAN AND FINDING DESCRIPTION

** FROM PREVIOUS PAGE **

	SEX: -----MALE-----				-----FEMALE-----			
	GROUP: -1-	-2-	-3-	-4-	-1-	-2-	-3-	-4-
NUMBER:	50	50	50	50	50	50	50	50
EPIDIDYMIDES (EP) NUMBER EXAMINED:	50	39	41	50	0	0	0	0
--S-B/METASTATIC NEOPLASM	0	1	0	0	0	0	0	0
PROSTATE (PR) NUMBER EXAMINED:	49	39	38	49	0	0	0	0
--ACUTE/SUBACUTE INFLAMMATION	10	8	8	9	0	0	0	0
--EPITHELIAL HYPERPLASIA	7	0	0	0	0	0	0	0
--CHRONIC INFLAMMATION	0	0	0	1	0	0	0	0
SEMINAL VESICLES (SV) NUMBER EXAMINED:	49	40	37	49	0	0	0	0
--ACCUMULATION OF SECRETORY MATERIAL	4	4	0	2	0	0	0	0
--DECREASE OF SECRETORY MATERIAL	0	4	3	1	0	0	0	0
--ACUTE/SUBACUTE INFLAMMATION	0	2	1	4	0	0	0	0
OVARIES (OV) NUMBER EXAMINED:	0	0	0	0	49	30	38	50
--U/CYST(S)	0	0	0	0	12	6	7	17
--B/CYST(S)	0	0	0	0	1	1	4	5
--S-U/GRANULOSA/THECA CELL TUMOR	0	0	0	0	1	0	0	1
--B/CONGESTION	0	0	0	0	0	0	0	1
--S-B/METASTATIC NEOPLASM	0	0	0	0	0	9	1	0
--U/HEMATOCYST	0	0	0	0	0	0	1	0
UTERUS (UT) NUMBER EXAMINED:	0	0	0	0	49	31	39	50
--ENDOMETRIAL CYST(S)	0	0	0	0	8	3	9	6
--LUMEN:DILATION	0	0	0	0	1	3	0	3
--ADENOMYOSIS	0	0	0	0	1	0	0	0
--ENDOMETRIUM:PIGMENT	0	0	0	0	1	0	0	0
--S-METASTATIC NEOPLASM	0	0	0	0	0	0	1	1
--H-ENDOMETRIAL STROMAL SARCOMA	0	0	0	0	0	0	0	2
--ACUTE INFLAMMATION/NECROSIS	0	0	0	0	0	0	1	3
--B-ENDOMETRIAL POLYP	9	0	0	0	1	0	3	4
--B-ENDOMETRIAL ADENOMA	0	0	0	0	0	0	0	1
--CERVIX:BOUNDOUS CELL HYPERPLASIA	0	0	0	0	0	0	1	2
--B-FIBROMA	0	0	0	0	0	0	0	1
--CERVIX:KERATINOUS CYST(S)	0	0	0	0	0	0	2	0
--ENDOMETRIUM:HEMATOCYST	0	0	0	0	0	0	1	0
PITUITARY GLAND (PG) NUMBER EXAMINED:	49	44	38	50	50	49	48	49
--B-PARS DISTALIS:ADENOMA	22	23	22	22	41	43	44	35
--HEMORRHAGE/HEMATOCYSTS	15	20	18	14	35	36	40	39

** CONTINUED ON NEXT PAGE **

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Control Data for Sprague-Dawley Rats
Long Term Studies

Females

STUDY I.D.	AA	BB	CC	DD	EE	FF	II	JJ	KK
DURATION OF STUDY IN MONTHS	24	24	24	24	24	24	24	24	24
Number Examined	70	80	70	70	80	65	49	68	60
<u>Tissue/finding (Uterus)</u>									
B-Endometrial polyp ¹	4	4	3	-	7	2	1	6	1
B-Cervix: stromal polyp	1	-	-	-	-	-	-	-	-
B-Polyp/benign tumor	-	-	-	1	-	-	-	-	-
B-U/Adenoma	-	-	-	1	-	-	-	-	-
M-Endometrial stromal sarcoma	-	1	-	-	1	-	-	-	-
M-Leiomyosarcoma	-	-	-	-	-	1	-	-	-
M-Endometrial adenocarcinoma	-	1	-	-	-	-	-	-	-
S-Metastatic/invasive neoplasm	-	-	-	-	1	-	-	-	-

¹This finding can also be found listed as endometrial stromal polyp.

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(3) MECHANISTIC STUDIES/HYPOTHESES

Remeron is considered to be non-genotoxic (see Dr. Sparenborg's review). The sponsor hypothesizes that the increase in liver tumors (seen in both mice and rats) is related to hepatic enzyme induction, and that the increase in thyroid follicular tumors (seen in male rats) is secondarily related to this induction via an increased glucuronidation and elimination of thyroxine, leading to a compensatory increase in TSH release by the pituitary and subsequent stimulation of the thyroid gland. Such a mechanism has also been suggested for other drugs, e.g. phenobarbital.

Studies in male mice and male rats showed that Remeron induces hepatic microsomal enzymes (including that responsible for glucuronidation of T_4) at doses equal to the HDs used in the carcinogenicity studies. (One of the rat studies was included in the submission of 9/28/95, and was not previously reviewed). (One previously reviewed rat study also showed enzyme induction in females; however the strain [Wistar] was different from that in the CA study, and the dose [80 mg/kg] was greater than the HD in the CA study and was given by gavage).

Three studies were performed in male rats to assess drug effects on blood TSH, T_3 , and T_4 ; the durations were 2 weeks (60 mg/kg in diet [i.e. the HD in the CA study]), 28 days (60 and 120 mg/kg in diet), and 90 days (60 mg/kg in diet or by gavage). (The 28 day study was submitted 9/28/95 and not previously reviewed; results are attached). Results across these 3 studies were inconsistent, although when effects were seen were generally in the direction supportive of the sponsor's hypotheses (i.e. increases in TSH and decreases in T_4). However, when these effects were seen they did not always occur in the same study (e.g. in the 2 week study slight decreases in T_4 were seen without change in TSH; in the 90 day study there was a slight increase in TSH but no change in T_4). Also, effects were only seen on some of the sampling days, e.g. in the 28 day study there was both an increase in TSH and a decrease in T_4 , but only on day 15 (with no effects on days 5 and 29). Individual animal data often showed a large amount of variability which is expected of hormonal measurements and probably contributed to the difficulty of showing a more consistent drug effect (if such an effect exists).

Even assuming that Remeron induces microsomal enzymes and (although less convincingly shown) decreases T_4 and increases TSH in the species tested, there are still some missing links in the sponsor's argument: primarily, that there is no evidence that these mechanisms were responsible for the liver and thyroid tumors observed (i.e., it is possible that the biochemical effects and tumorigenic effects were independent effects of the drug and not related to each other). (For some drugs, e.g. phenobarbital, there is more evidence for this relationship, e.g. administering exogenous T_4 decreases the thyroid tumorigenic response.). Also it is not clear why female rats did not develop thyroid tumors, even though the liver tumorigenic effect appeared to be greater in females. (Perhaps females did not have decreases in T_4

and increases in TSH; however, this was not looked at in females). Overall, although the sponsor's proposed mechanisms are plausible (in part based on previous work with other drugs), and are supported by some (albeit somewhat inconsistent) data, there is still some uncertainty regarding their operation in mice and rats. More importantly, it is not clear if it has been shown that the same mechanisms would not be operative in humans receiving therapeutic doses. (At the CAC meeting of 11/16/95, the sponsor stated that liver enzyme induction is not seen in humans "as evident by the linear kinetics from 15/30 mg - 75 mg;" however this does not prove lack of induction, which would involve monitoring for a change in plasma levels with repeated dosing; also, it is possible for a drug to induce enzymes responsible for the metabolism of other compounds but not of the drug itself. The sponsor also mentioned that a human study showed no drug effects on thyroid hormone or TSH levels, but no results were shown [and note that, as mentioned above in connection with the animal studies, such effects are hard to show]. [It is noted that if a drug-induced increase in TSH does occur in humans, there is some controversy regarding whether increased TSH is associated with thyroid tumors in humans-see Hill, et. al. Fundam. Appl. Tox. 12: 629-697, 1989]).

Determination of TSH, T3 and T4 Levels in Serum of Rats Administered
ORG 3770 via the Diet over a Period of 28 Days

Day 5				
	Rat #	TSH (ng/ml)	T4 (ug/dl)	T3 (ng/dl)
STAT SYMBOL:		A-L-	A-L-	A-L-
CONTROL	GROUP I			
	a	5	3.17	3.32
	a	6	3.10	4.58
	b	29	2.78	3.86
	b	30	4.41	5.48
	c	53	2.50	4.77
	c	54	2.32	4.78
	Mean	3.05	4.47	94.61
	SD	0.74	0.76	7.51
	N	6	6	6
60 mg/kg	GROUP III			
	a	17	2.06	3.74
	a	18	6.25	2.87
	b	41	2.20	4.63
	b	42	1.57	7.38
	c	65	2.64	4.22
	c	66	2.09	7.28
	Mean	2.80	5.02	94.87
	SD	1.72	1.88	12.14
	N	6	6	6
120 mg/kg	GROUP IV			
	a	23	5.56	2.67
	a	24	2.58	4.65
	b	47	3.68	4.06
	b	48	3.99	3.07
	c	71	1.49	5.90
	c	72	4.67	4.89
	Mean	3.66	4.21	93.60
	SD	1.46	1.20	18.40
	N	6	6	6



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93-2293

Determination of TSH, T3 and T4 Levels in Serum of Rats Administered
ORG 3770 via the Diet over a Period of 28 Days

Day 15				
	Rat #	TSH (ng/ml)	T4 (ug/dl)	T3 (ng/dl)
STAT SYMBOL:		KJ+	A+L+	A-L-
GROUP I				
a	3	2.27	5.12	107.86
a	4	1.51	4.70	112.30
b	27	1.31	5.65	92.47
b	28	1.81	4.24	86.87
c	51	1.87	5.47	83.66
c	52	2.46	5.03	98.10
	Mean	1.87	5.04	96.88
	SD	0.44	0.51	11.44
	N	6	6	6
GROUP III				
a	15	1.69	3.04	78.49
a	16	3.44	3.60	84.82
b	39	4.22	4.63	69.86
b	40	4.72	3.90	81.95
c	63	1.53	5.50	110.99
c	64	3.29	4.75	104.80
	Mean	3.15	4.24	88.49
	SD	1.30	0.89	15.97
	N	6	6	6
GROUP IV				
a	21	3.60	5.23	95.19
a	22	3.70	4.34	98.33
b	45	2.94	3.72	88.28
b	46	5.45	3.96	99.98
c	69	10.49	2.74	64.89
c	70	6.10	3.45	96.59
	Mean	5.38*	3.57**	90.54
	SD	2.78	0.56	13.20
	N	6	6	6



ORGANON Inc.

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LSR 1/932346

93-2293

Determination of TSH, T3 and T4 Levels in Serum of Rats Administered
ORG 3770 via the Diet over a Period of 28 Days

Day 29				
	Rat #	TSH (ng/ml)	T4 (ug/dl)	T3 (ng/dl)
STAT SYMBOL:		A-L-	A-L-	A-L-
GROUP I a a b b c c	1	2.56	2.20	68.72
	2	1.46	5.59	88.15
	25	2.92	4.44	93.94
	26	3.80	4.54	75.20
	49	3.07	5.05	72.15
	50	3.21	5.38	79.54
	Mean	2.84	4.53	79.62
	SD	0.79	1.23	9.72
	N	6	6	6
GROUP III a a b b c c	13	4.41	3.42	96.71
	14	2.95	3.94	101.68
	37	2.65	2.83	93.74
	38	3.33	5.50	83.40
	61	3.98	4.42	89.75
	62	2.40	3.88	81.50
	Mean	3.29	4.00	91.13
	SD	0.76	0.91	7.79
	N	6	6	6
GROUP IV a a b b c c	19	2.78	3.69	101.19
	20	1.53	4.52	82.48
	43	7.01	2.03	71.54
	44	5.22	3.93	87.06
	67	2.48	3.56	73.96
	68	5.19	4.38	98.64
	Mean	4.04	3.69	85.81
	SD	2.09	0.89	12.31
	N	6	6	6

CONTROL

60
mg/kg120
mg/kg

LABELING:

Dr. Sparenborg included suggested labeling regarding the carcinogenicity study results in his review of 9/20/95. The tumor types mentioned were "hepatocellular adenoma/carcinoma" in male mice, "hepatocellular adenoma" in female rats, and "thyroid follicular cell adenoma/cystadenoma/carcinoma" in male rats. It is stated that "These effects are presumed to be due to liver enzyme induction and are not likely to be genotoxic responses" and that "The relevance of these findings to humans is unknown." Dr. Sparenborg indicated that the suggested labelling may have to be changed based on further information being requested from the sponsor, e.g. historical control data. Based on my re-evaluation of the studies, including the newly submitted data (9/28/95), I concur with mentioning the above tumors in the labeling, although I think the doses at which they occurred should be included. In addition, I recommend that the findings suggestive of an increase in male rat liver tumors be added; although the numbers of tumors are not striking, I believe they are drug related as discussed in detail above. Also, since it is current policy to include comparative exposure data in the labeling, this information may need to be included if the data are considered to be reliable. (As noted above, the mouse/human AUC ratio was said to be about 1 [at the HD in the CA study]; these data have not as yet been submitted to the Agency for a determination of their validity [also note that data was shown only for parent compound, whereas this drug is extensively metabolized]).

The question of whether to mention that the doses in the mouse study were inadequate is deferred pending further discussion by the review team (and pending submission of exposure data which may bear on this issue).

Regarding the proposed mechanisms of tumorigenesis, as discussed above I think they are plausible but not well-established and thus I do not think the phrase "these effects are presumed to be due to liver enzyme induction..." should be used.

Suggested labeling is as follows:

Carcinogenesis: Carcinogenicity studies were conducted with mirtazapine given in the diet at doses of 2, 20, and 200 mg/kg/day in mice and 2, 20, and 60 mg/kg/day in rats. The highest doses used are 22 and 13 times the maximum recommended human dose on a mg/m² basis in mice and rats, respectively. There was an increased incidence of hepatocellular adenoma and carcinoma in male mice receiving 200 mg/kg/day, of hepatocellular adenoma in female rats receiving 20 and 60 mg/kg/day (with a trend toward increased hepatocellular tumors in male rats receiving 60 mg/kg/day), and of thyroid follicular adenoma/cystadenoma and carcinoma in male rats receiving 60 mg/kg/day (with a trend toward an increase in adenoma/cystadenoma at the lower doses). The data suggest that the above effects may be mediated by non-genotoxic mechanisms, the relevance of which to humans is not known.

RECOMMENDATIONS:

- 1) See recommendations regarding proposed labeling, above.
- 2) To help determine the acceptability of the mouse carcinogenicity study (i.e. regarding dosage adequacy), the sponsor should be requested to submit the data on mouse plasma drug levels which were presented at the CAC meeting on 11/16/95. Since the drug is extensively metabolized, data on relative (i.e. between mouse and human) exposure to metabolites would also be useful. (These exposure data, if adequate, should also be incorporated into the labeling as noted earlier).



Barry N. Rosloff, Ph.D.

cc: HFD-120/Div. File

/BRosloff

/GFitzgerald 497 12/14/95

/PDavid

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Labeling should include statement about inadequacy of mouse doses in carcinogenicity study.

Statistical Review and Evaluation

NDA #: 20-415

Date: JUN 30 1995

Applicant: Organon Inc.

Name of Drug: Remeron (Mirtazapine) Tablets

ACTION

Documents Reviewed:

JUN 30 1995

1. NDA submission volumes 2.28 to 2.31 "An Eighteen Month Carcinogenicity Feeding Study in Mice With ORG 3770", March 13, 1989, Date of Documents, Jan. 30, 1995.
2. NDA submission volumes 2.32 to 2.36 "A Twenty-Four Month Feeding Study in Rats With ORG 3770", May 11, 1990, Date of Documents, Jan. 30, 1995.
3. Special Submission, Amendments and Data diskettes for Carcinogenicity studies, Date of Document, Nov. 18, 1994.
4. NDA original amendments, Data diskettes and computer listings of Carcinogenicity studies, Date of Document, May 3, 1995.

I. Background

Two animal carcinogenicity studies (one in rats and one in mice) were included in this NDA submission. The purpose of these studies was to assess the carcinogenic potential of Remeron (Org 3770) when administered orally, via dietary admixture, to rats and mice for 24 and 18 months, respectively. Mr. Paul David, HFD-120, who is the reviewing CSO of this NDA has requested the Division of Biometrics to perform the statistical review and evaluation of these two studies.

II. The Rat StudyII. a. Design

In this study, Org 3770 was administered orally, via dietary admixture, to 300 Sprague-Dawley CD rats (50/sex/group) at dose levels of 2, 20, and 60 mg/kg/day for twenty-four months. Additional groups of 50 animals/sex received standard laboratory diet and treated as controls. Physical observations, body weight and food consumption measurements were performed on all animals pretest and at selected intervals during the treatment period. After at least twenty-four months of treatment, all survivors were sacrificed. Complete gross postmortem examinations were performed on all animals. Histopathological evaluations of selected tissues were conducted on all animals in the control and high-dose groups as well as all animals dying before study termination. In addition, livers and thyroid glands of all animals in the mid- and low-dose groups were evaluated. This study started March 13, 1986 and ended March 21-23, 1988.

II. b. Sponsor's Analyses

No statistical analysis was performed on the survival data. Based on the summary data in Tables 1 and 2, the sponsor indicated that mortality data did not reveal any indications of adverse treatment-related effects between the control and treated animals.

A standard chi-square analysis was performed to determine if the proportions of incidence differed between the groups tested. The 2x2 Fisher Exact test was used to compare each treatment group with the control group. The p-values were corrected via the Bonferroni inequality to assure a prespecified overall type I error rate. The Armitage test was used to test the linear trend in tumor rates. If the 2x4 table had an expected value less than 5, the results of the chi-square and the Armitage tests were not reported. When this occurred, only the Fisher Exact test (corrected via Bonferroni inequality) was performed and reported. All tests were performed at the 5% and 1% levels of significance. The results of the above analyses showed that the incidences of thyroid follicular cells adenoma/cystadenoma and carcinomas were statistically significantly higher in the high dose males when compared to controls. The higher incidence of thyroid follicular cell neoplasms in the high dose group is known to occur in rats when treated with enzyme inducer compounds, like ORG-3770. Table 3 listed the selected findings in the thyroid gland for male and female rats.

Based on the above analyses, the sponsor concluded that "the results of gross and microscopic postmortem examination showed an increase of thyroid follicular cell neoplasms in treated rats, compared to the respective controls."

II.c. Reviewer's analyses and Comments

The Cox test and the generalized Wilcoxon test described in the paper of Thomas, Breslow, and Gart ("Trend and Homogeneity Analyses of Proportions and Life Table Data", Computers and Biomedical Research, 10, 373-381, 1977) were used to test for heterogeneity in survival distribution. The p-values of the Cox test were 0.0038 and 0.2316 for males and females, respectively. Hence, there was no statistically significant difference (at 0.05 level) in survival distribution in female rats. However, there was a statistically significant difference in survival distribution in male rats. A similar conclusion was obtained in the generalized Wilcoxon test. The p-values were 0.0080 and 0.1469 for males and females, respectively.

The intercurrent mortality rates for both male and female rats (see Table 4) were tested for linear trend according to the death rate method described in the paper of Peto et al. ("Guidelines for Simple, Sensitive Significance Tests for Carcinogenic Effects in Long-Term Animal Experiments", In Long-Term and Short-Term Screening Assays for

Carcinogens: A Critical Appraisal, International Agency for Research on Cancer Monographs, Annex to Supplement 2, World Health Organization, 311-426, 1980) using the time intervals 0-50, 51-80, and 81-105 weeks. The actual dose levels 0, 2, 20, and 60 mg/kg/day were the scores assigned to the control, low, medium, and high dose groups, respectively. The results of the analyses showed that there was no significant (at 0.05 level) linear trend in the intercurrent mortality rate in female rats ($p = 0.1859$). However, there was a significant (at 0.05 level) linear trend in the intercurrent mortality rate in male rats ($p = 0.0007$).

The methods described in Peto et al. (1980) and the methods of exact permutation trend test were used to test the linear trend in the tumor data. Noted that some tissues were not histologically examined on all of the animals. Due to the limitation of the data submitted by the sponsor, the age-adjusted method was applied only to the tissues with all of the animals or more than 98% of animals examined microscopically. The age-unadjusted method was applied to some of the tumor/organ combinations to which the age-adjusted method can not be applied. The results of the above analyses showed that there was a significant (at 0.05 level) positive linear trend in the following neoplastic lesions:

(1) Liver hepatocellular adenoma (age-adjusted: $p = 0.0262$), thyroid gland follicular cell adenoma/cystadenoma (age-adjusted: $p = 0.0153$; age-unadjusted: $p = 0.0045$), and thyroid gland follicular cell carcinoma (age-adjusted: $p = 0.1067$; age-unadjusted: $p = 0.0383$) in males.

(2) Liver hepatocellular adenoma (age-adjusted: $p = 0.008$) and uterus endometrial polyp (age-adjusted: $p = 0.0347$; age-unadjusted: $p = 0.0639$) in females.

The statistical test results also showed that there are marginally significant (at 0.05 level) positive linear trends in uterus endometrial stromal sarcoma (age-adjusted: $p = 0.0731$; age-unadjusted: $p = 0.0863$) in females and in parathyroid GLS. adenoma (age-adjusted: $p = 0.1611$; age-unadjusted: $p = 0.0594$) in males.

The incidence rates of the above tumor types are listed as follows:

Tumor/organ	Incidence of Tumors				P-values	
					Unadjusted	adjusted
Males:						
Liver:						
Hepatocellular Adenoma						
	(50)	(50)	(50)	(50)		
	0	0	0	3		0.0262

Parathyroid GLS.:

Adenoma

(46)	(48)	(44)	(45)		
0	0	0	2	0.0594	0.1611

Thyroid Gland:

Follicular Cell Adenoma/Cystadenoma

(48)	(49)	(50)	(46)		
1	4	5	9	0.0045*	0.0153

Thyroid Gland:

Follicular Cell Carcinoma

(48)	(49)	(50)	(46)		
0	1	1	3	0.0383	0.1067

Females:

Liver:

Hepatocellular Adenoma

(50)	(50)	(50)	(50)		
0	0	4	5		0.008*

Uterus:

Endometrial Stromal Sarcoma

(49)	(31)	(39)	(50)		
0	0	0	2	0.0863	0.0731

Uterus:

Endometrial Polyp

(49)	(31)	(39)	(50)		
1	0	3	4	0.0639	0.0347

In order to reduce the overall false positive rate, the following decision rule was used to adjust the effect of multiple testings. A positive linear trend is considered not to occur by chance of variation alone if the p-value is less than 0.005 for a common tumor, and 0.025 for a rare tumor.

On the basis of the above rule, the linear trends with the p-values marked with asterisks in the above table are considered to be statistically significant.

The pairwise comparisons between the high dose and control groups were performed on the tumors with statistically significant trend tests. The results showed that no significantly higher incidence rates in the high dose vs control groups in liver hepatocellular adenoma ($p = 0.0347$) in females or in thyroid gland follicular cell adenoma/cystadenoma ($p = 0.0406$) in males.

Noted that the numbers of thyroids examined given in the sponsor's report (volume 2.32, P. 0131) are 45, 35, 41, and 46 for control, low, medium, and high dose males. However, the sponsor's another report (volume 2.35, P. 0465) listed the numbers of thyroids examined as 48, 49, 50, and 46 for control, low, medium, and high dose males. Similarly, the incidence rates of thyroid gland follicular cell adenoma/cystadenoma given in the sponsor's report (volume 2.32, P. 0131) are 1, 4, 4, and 9 for control, low, medium, and high dose males. However, the reviewer found that the incidence rates of this tumor are 1, 4, 5, and 9, for the four groups, respectively from the sponsor's another report (volume 2.35, P. 0465) and from the sponsor's submitted computer diskettes. In this review, the data included in the sponsor's submitted computer diskettes are used for analysis.

III. The Mouse Study

III. a. Design

In this study, 200 male and 200 female CD-1 mice were randomly distributed into four groups (50/sex/group). Animals in groups 2, 3, and 4 received Org 3770 orally via dietary admixture (Purina Certified Rodent Chow No. 5002) at dose levels of 2.0, 20.0, or 200.0 mg/kg/day, respectively, for eighteen months. Animals in group 1, the controls, were similarly dosed with the vehicle only. Physical observations, body weight and food consumption measurements were performed on all animals pretest and at selected intervals during the treatment period. After at least eighteen months of treatment, all survivors were sacrificed. Complete gross postmortem examinations were performed on all animals. Histopathological evaluations of selected tissues were conducted on all animals in the control and high-dose groups as well as all animals dying before study termination. In addition, gross lesions were examined for all animals in the study and the livers from all male animals only were microscopically examined. Samples of the livers from 12 male animals (3 per group) were sent to experimental pathology laboratories, Inc. for electron microscopy. This study started September 3, 1985 and ended March 4-10, 1987 (Depending on the day of sacrifice).

III. b. Sponsor's Analyses

No statistical analysis was performed on the survival data. Based on the summary data in Table 5, the sponsor indicated that mortality was similar between all treatment groups and control groups at termination of the study.

Similar to the rat study, the chi-square test, the Fisher Exact test, and the Armitage trend test were used to analyze the tumor data. All tests were performed at the 5% and 1% level of significance. The results of the above analyses showed that there was a statistically significantly increased incidence of hepatocellular adenomas/carcinoma combined in the high dose males only ($p < 0.05$).

The sponsor stated that "from results obtained in other toxicological studies and the literature, it is suggested that the increased incidence of hepatocellular tumors in the male mice of the high dose group is a non-genotoxic response associated with hepatocytic microsomal induction; a well known phenomenon in the mouse liver reported in the literature for a wide variety of compounds". A summary of neoplastic findings is presented in Table 6. The sponsor indicated that "all other findings were considered to be spontaneous or iatrogenic and not related to the exposure of animals to the compound Org 3770."

III.c. Reviewer's analyses and Comments

The Cox test and the generalized Wilcoxon test were used to test for heterogeneity in survival distribution. The p-values of the Cox test were 0.6839 and 0.9226 for males and females, respectively. Hence, there was not statistically significant differences (at 0.05 level) in survival distribution in both sexes. A similar conclusion was obtained in the generalized Wilcoxon test. The p-values were 0.6496 and 0.9140 for males and females, respectively.

The intercurrent mortality rates for both male and female mice (see Table 7) were tested for linear trend using the time intervals 0-50 and 51-78 weeks. The results of the analyses showed that there was no significant (at 0.05 level) linear trend in the intercurrent mortality rate in both males ($p = 0.3956$) and females ($p = 0.2613$).

The methods described in Peto et al. (1980) and the methods of exact permutation trend test were used to test the linear trend in the tumor data. Noted that some tissues were not histologically examined on all of the animals. Due to the limitation of the data submitted by the sponsor, the age-adjusted method was applied only to the tissues with all of the animals or more than 98% of animals examined microscopically. The age-unadjusted method was applied to some of the tumor/organ combinations to which the age-adjusted method can not be applied. The results of the above analyses showed that there were significant (at 0.05 level) positive linear trends in the following neoplastic lesions:

(1) Lung alveologenic adenoma (age-adjusted: $p = 0.017$; age-unadjusted: $p = 0.0425$) in females.

(2) Liver hepatocellular adenoma (age-adjusted: $p = 0.0056$) and liver hepatocellular carcinoma (age-adjusted: $p = 0.0413$) in males.

The statistical test results also showed that there is a marginally significant (at 0.05 level) positive linear trend in uterus endometrial stromal polyp (age-adjusted: $p = 0.0759$; age-unadjusted: $p = 0.0944$) in females.

The incidence rates of the above tumor types are listed as follows:

Tumor/organ	Incidence of Tumors				P-values	
					Unadjusted	adjusted
Males:						
Liver:						
Hepatocellular Adenoma	(50)	(50)	(50)	(50)		
	3	3	6	10		0.0056
Liver:						
Hepatocellular Carcinoma	(50)	(50)	(50)	(50)		
	4	2	5	8		0.0413
Females:						
Lung:						
Alveologenic Adenoma	(50)	(25)	(25)	(50)		
	1	0	0	4	0.0425	0.017
Uterus:						
Endometrial Stromal Polyp	(49)	(38)	(36)	(50)		
	1	0	2	3	0.0944	0.0759

In order to reduce the overall false positive rate, the following decision rule was used to adjust the effect of multiple testings. A positive linear trend is considered not to occur by chance of variation alone if the p-value is less than 0.005 for a common tumor, and 0.025 for a rare tumor. On the basis of the above rule, no dose-related trend was detected in both sexes.

The reviewer also evaluated the validity of the experiment. The following two issues are important in determining the validity of an experiment: (1) The numbers of animals alive over the course of the study to get an adequate exposure to the chemical and to be at risk of forming late-developing tumors. (2) If the doses are high enough to present a reasonable tumor challenge to the animals.

With regard to the first issue, the following criteria or rules of thumb have been proposed by some experts in the field:

(A) Haseman proposes (through personal communication with Dr. Karl Lin) that a 50% survival rate of the 50 initial animals in the high dose group between weeks 80-90 will be considered as a sufficient number and an adequate exposure. However, the percentage can be lower or higher if the number of animals used in each treatment/sex is larger or smaller than 50 as long as there will be between 20 to 30 animals still alive during these weeks.

(B) Chu, Ceuto, and Ward ("Factors in the Evaluation of 200 National Cancer Institute Carcinogen Bioassays", Journal of Toxicology and Environmental Health, 8, 1981, pp. 251-280) propose that an experiment that has not shown a chemical to be carcinogenic should have (high dose) groups of animals with greater than 50% survival at one year (52 weeks).

In this study, the survival rates of the high dose mice at one-year were 96% and 98% for males and females, respectively. These one-year survival rates satisfy the criterion of Chu et al. (1981). The survival rates of the control, low, medium, and high dose mice in the terminal sacrifice were 52%, 50%, 60%, and 50%, respectively, for males, and 54%, 50%, 52%, and 56%, respectively, for females. There were sufficient mice in the treated groups living long enough to get an adequate exposure to the chemical and to be at risk of forming late-developing tumors based on Haseman's proposition.

With regard to the second issue, in the paper of Chu, Ceuto and Ward (1981), the following criteria for dose adequacy are mentioned.

(A) "A dose is considered adequate if there is a detectable loss in weight gain of up to 10% in a dosed group relative to the controls."

(B) "The administered dose is also considered an MTD (Maximum Tolerated Dose) if dosed animals exhibit clinical signs or severe histopathologic toxic effects attributed to the chemical."

(C) "In addition, doses are considered adequate if the dosed animals show a slightly increased mortality compared to the controls."

Figures 1 and 2 plotted the mean body weight versus time in weeks for males and females, respectively. In Tables 8-9, summaries of mean body weight data of the male and female mice are given. The body weight gains in the male low and medium dose groups are 3.38% and 0.84%, respectively, more than that of the male control group. However, the body weight gains in the male high dose group are 13.55% less than that of the male control group. The body weight gains in the female low, medium, and high dose groups are 3.03%, 3.78%, and 9.84%, respectively, less than that of the female control group.

It seems that the high dose is close to MTD based on body weight gain and mortality data. However, before drawing the final conclusion on the appropriateness of the selected high dose, the clinical and toxic signs of the treated animals still need to be checked.

IV. Summary

IV.a. The Rat Study

The test results revealed that there was no statistically significant difference in survival distribution in female rats. However, there

was a statistically significant difference in survival distribution in male rats. Applying Peto's method to test the positive linear trend in intercurrent mortality rates, the results of the analyses showed that there was no significant linear trend in the intercurrent mortality rate in female rats. However, there was a significant linear trend in the intercurrent mortality rate in male rats ($p = 0.0007$).

The Peto and the exact permutation trend tests were used to test the positive linear trend in the tumor data. Noted that some tissues were not histologically examined on all of the animals. Due to the limitation of the data submitted by the sponsor, the age-adjusted method was applied only to the tissues with all of the animals or more than 98% of animals examined microscopically. The age-unadjusted method was applied to some of the tumor/organ combinations to which the age-adjusted method can not be applied. The results of the above analyses showed that there was a significant (at 0.05 level) positive linear trend in the thyroid gland follicular cell adenoma/cystadenoma (age-adjusted: $p = 0.0153$; age-unadjusted: $p = 0.0045$) in males, and in liver hepatocellular adenoma (age-adjusted: $p = 0.008$) in females.

IV.b. The Mouse Study

The test results revealed that there was no statistically significant differences in survival distribution, and linear trend in intercurrent mortality rate in both sexes. Results of tumor data analyses showed that there is no dose-related trend (at 0.005 level for a common tumor, and at 0.025 level for a rare tumor) in male and female mice.

The results of analyses of body weight gain and mortality show that the high dose used is close to MTD. However, before drawing the final conclusion on the appropriateness of the selected high dose, the clinical and toxic signs of the treated animals still need to be checked.

Daphne L

Daphne Lin, Ph.D.
Mathematical Statistician

Concur:

Karl K. Lin 6/30/95
Karl K. Lin, Ph.D., Group Leader, SARB

cc: Original NDA 20-415
HFD-120/Dr. Leber
HFD-120/Dr. Fitzgerald
HFD-120/Dr. Sparenborg
HFD-120/Mr. P. David

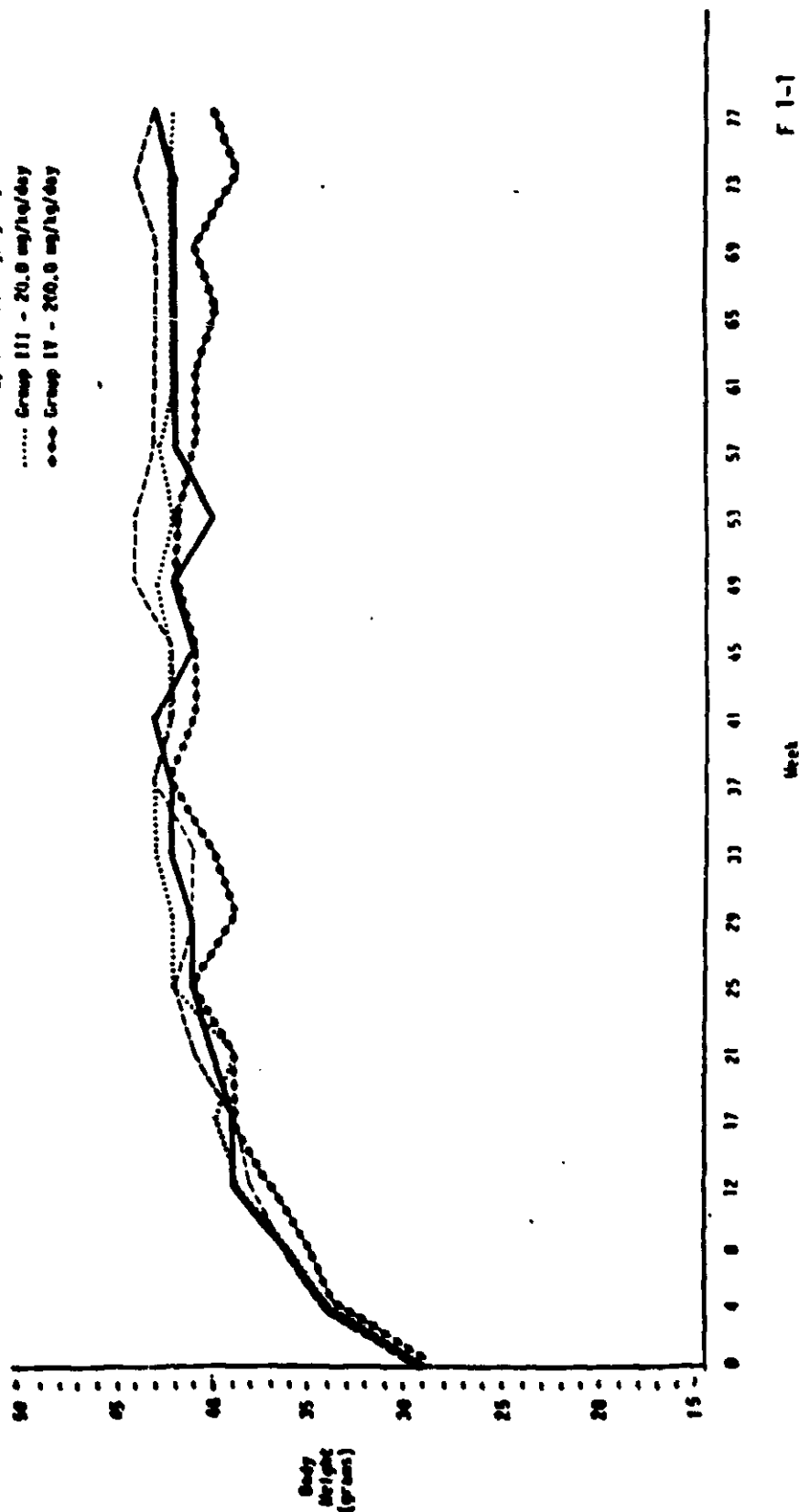
Figure 1

85-2939

Figure 1
An Eighteen Month Carcinogenicity Feeding Study
in Mice with Org 3770

Graphic Representation of Mean Body Weight Data
Males

- Group I - 0 mg/kg/day
- - - Group II - 2.0 mg/kg/day
- Group III - 20.0 mg/kg/day
- o-o-o Group IV - 200.0 mg/kg/day



F 1-1

Week

0025

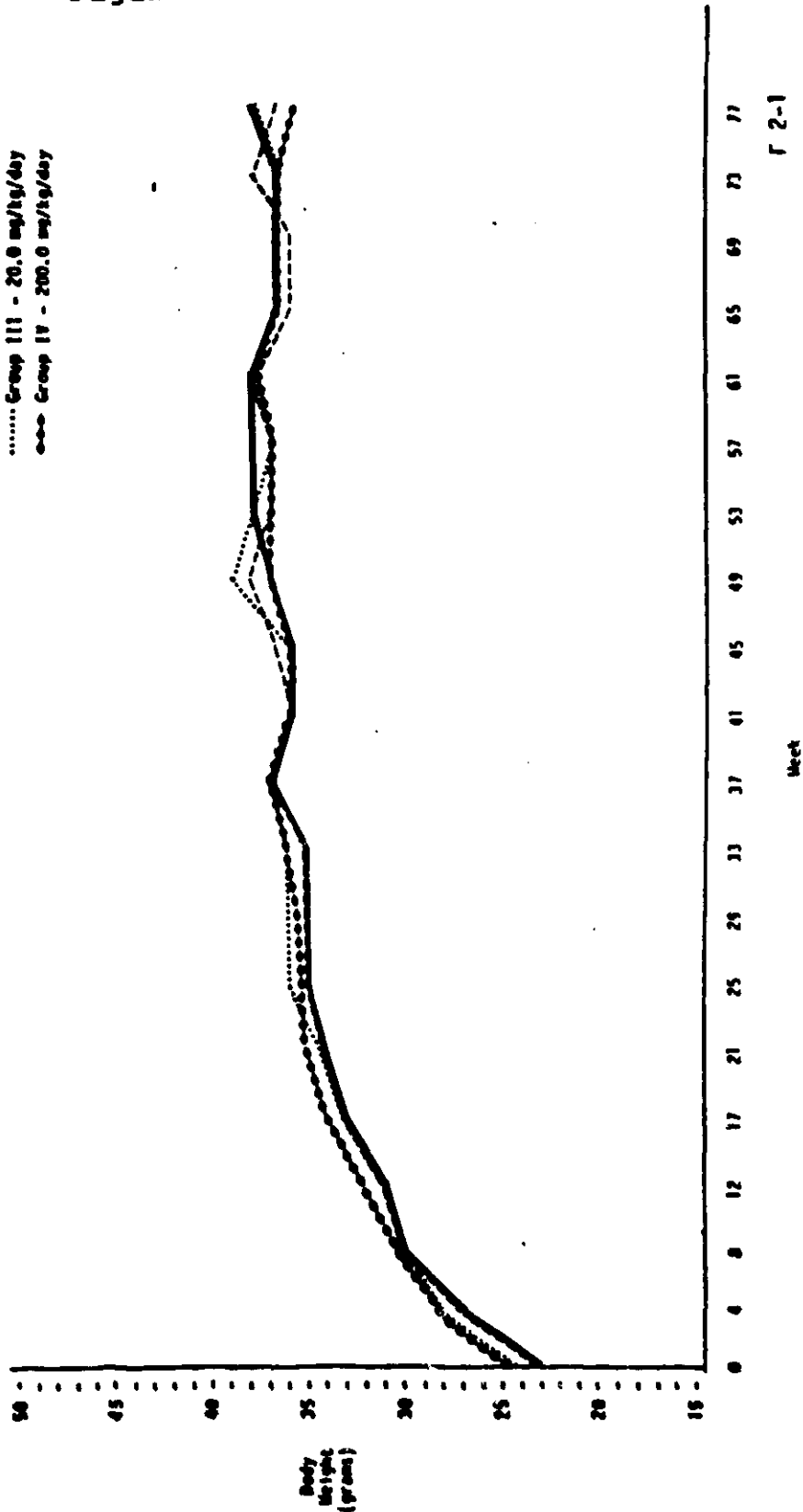
Figure 2

85-2939

Figure 2
An Eighteen Month Carcinogenicity Feeding Study
in Mice with Org 3770

Graphic Representation of Mean Body Weight Data
Females

- Group I - 0 mg/kg/day
- - - Group II - 2.0 mg/kg/day
- Group III - 20.0 mg/kg/day
- o-o-o Group IV - 200.0 mg/kg/day



r 2-1

Week

Body Weight
(grams)

Table 1

85-2938

Appendix B
A Twenty-Four Month Feeding Study
in Rats with Org 3770

Mortality Summary^a

Initial Number on Test	Group mg/kg/day	Month: 1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	TOTAL	TOTAL	TOTAL	
																											50 & M	A	ALL	
Males																														
50	I	1	0	1	0	1	0	0	0	0	0	0	0	1	2	0	0	3	1	3	0	1	2	0	3	1	35	0	35	
50	II	0	1	0	0	0	0	0	0	0	0	0	0	0	2	1	1	1	1	3	3	5	0	5	3	2	1	36	0	36
50	III	0	0	0	0	0	0	0	0	0	0	0	0	1	2	2	2	1	4	3	4	5	5	3	2	1	35	2	37	
50	IV	0	0	1	0	0	0	0	0	0	0	0	1	1	0	0	2	0	0	3	3	2	1	4	2	2	22	0	22	
Females																														
50	I	0	0	0	0	0	0	0	0	1	0	0	0	0	0	1	2	2	0	5	1	5	4	2	2	0	26	0	26	
50	II	0	0	0	0	0	0	0	0	0	0	0	3	1	1	2	3	3	3	0	5	4	2	3	2	0	29	0	29	
50	III	0	0	0	0	0	0	0	1	0	0	0	0	0	0	1	1	2	5	1	5	6	2	5	4	2	35	0	35	
50	IV	0	0	0	0	0	0	0	0	0	0	0	1	1	0	1	0	0	2	0	1	7	5	3	5	2	27	0	27	

^aIncludes animals dying spontaneously or sacrificed in a moribund condition. Animals dying accidentally are presented in parentheses.
Total 50 & M = Total animals dying spontaneously or sacrificed in a moribund condition.
Total A = Total animals dying accidentally.
Total ALL = Total of all unscheduled deaths (sum of Total 50 & M and Total A).

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ORGANON Inc.

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Table 2

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A Twenty-four Month Feeding Study
in Rats with Org 3770
Pathology Report

Figure 1

Mortality Summary

	Males				Females			
	I	II	III	IV	I	II	III	IV
Terminal sacrifice	15	14	13	28	24	21	15	23
Killed <u>in extremis</u>	10	14	12	8	12	16	23	14
Spontaneous deaths	25	22	23	14	14	13	12	13
Accidental deaths			2					
Total	50	50	50	50	50	50	50	50

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Table 3

A Twenty-four Month Feeding Study
in Rats with Org 3770
Pathology Report

Figure 2

Summary of Selected Findings in the Thyroid Gland

Thyroid Gland	Males				Females			
	I	II	III	IV	I	II	III	IV
Number of Thyroids Examined	48	35	41	46	50	30	37	49
Follicular Cell Adenoma/Cystadenoma	1	4	4	9*	1	1	1	1
Follicular Cell Carcinoma		1	1	3			1	
Combined	1	5	5	12**	1	1	2	1

* statistically significant difference (p. < 0.05)

** statistically significant difference (p. < 0.01)

Table 4
Intercurrent Mortality Rates
Male Rats

<u>Weeks</u>	<u>Control</u>			<u>Low</u>			<u>Medium</u>			<u>High</u>		
	S	D	%	S	D	%	S	D	%	S	D	%
0-50	50	4	8.0	50	1	2.0	50	0	0	50	1	2.0
51-80	46	7	15.2	49	10	20.4	50	17	34.0	49	6	12.2
81-105	39	24	61.5	39	24	61.5	33	19	57.6	43	13	30.2
Term.	15			15			14			30		

Peto Test: p-value = 0.0007

Female Rats

<u>Weeks</u>	<u>Control</u>			<u>Low</u>			<u>Medium</u>			<u>High</u>		
	S	D	%	S	D	%	S	D	%	S	D	%
0-50	50	1	2.0	50	0	0.0	50	1	2	50	0	0.0
51-80	49	7	14.3	50	13	26	49	9	18.4	50	4	8.0
81-105	42	18	42.9	37	16	43.2	40	24	60	46	22	47.8
Term.	24			21			16			24		

Peto Test: p-value = 0.1859

Notes: S: Number of animals starting during the period
 D: Deaths
 %: Percent of death during the period

Table 5

85-7939

Appendix B
An Eighteen Month Carcinogenicity Feeding Study
in Mice with Drg 3770

Mortality Summary^a

Group	mg/kg/day	Initial Number on test	Month: 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18																		TOTAL SD & M	TOTAL ALL	
			1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18			
Males																							
I	0	50	0	0	0	1	0	0	1	0	0	0	0	0	2	2	6	2	7	0	22	2	24
					(1)				(1)														
II	2.0	50	0	0	0	1	0	0	0	1	0	1	0	2	0	6	2	6	6	0	25	0	25
III	20.0	50	0	0	0	0	0	0	0	0	0	0	0	0	3	2	4	3	6	2	20	2	22
												(1)							(1)				
IV	200.0	50	0	0	0	0	0	0	0	0	0	0	1	0	2	3	6	5	7	0	24	1	25
												(1)											
Females																							
I	0	50	0	0	0	0	0	0	0	2	0	0	0	1	4	4	6	5	0	22	1	23	23
										(1)													
II	2.0	50	0	0	0	0	0	0	0	0	0	0	2	1	3	5	0	0	0	23	2	25	25
										(2)													
III	20.0	50	0	0	0	1	1	0	0	0	2	0	2	0	0	2	4	7	5	0	24	0	24
IV	200.0	50	0	0	0	0	0	1	0	0	0	0	0	3	4	6	6	4	2	20	0	20	20

^aIncludes animals dying spontaneously or sacrificed in a moribund condition. Animals dying accidentally are presented in parentheses.
Total SD & M = total animals dying spontaneously or sacrificed in a moribund condition.
Total A = total animals dying accidentally.
Total M.L. = total of all unscheduled deaths (sum of total SD & M and total A).

0-1

Table 6

F-950

PRINTED: 04-JAN-83
PAGE: 2

*** PATH/TON SYSTEM OUTPUT ***
AN EIGHTEEN MONTH CARCINOGENICITY FEEDING STUDY
IN NICE WITH DRC 3770
INCIDENCE SUMMARY

STUDY NUMBER: 852939

..... NUMBER OF ANIMALS AFFECTED

TABLE INCLUDES:
SEX=ALL; GROUP=ALL; SCREEN=ALL; WEEKS=ALL
DEATH=ALL; FIND=0, N, S; SUBSET=ALL

	SEX:	MALE:	FEMALE:	
	GROUP:	1 2 3 4	1 2 3 4	
ORGAN AND FINDING DESCRIPTION	NUMBER:	50 50 50 50	50 50 50 50	
.. TOP OF LIST ..				
BRAIN (BR)	NUMBER EXAMINED:	50 25 22 50	50 25 24 50	
CERVICAL SC (SC1)	NUMBER EXAMINED:	47 23 19 48	47 24 21 49	
NERVE SCIATIC (NE1)	NUMBER EXAMINED:	47 24 20 45	45 23 22 49	
HEART (HT)	NUMBER EXAMINED:	50 25 22 50	50 25 24 50	
TRACHEA (TR)	NUMBER EXAMINED:	48 24 22 50	48 24 23 47	
LUNGS (LW)	NUMBER EXAMINED:	50 30 24 50	50 25 25 50	
..B-ALVEOLOGENIC ADENOMA		0 0 1 1	0 0 0 4	
..N-ALVEOLOGENIC CARCINOMA		4 3 1 1	2 0 0 0	
MESENTERIC LN (LN1)	NUMBER EXAMINED:	46 28 20 49	48 29 20 49	
MEDIASTINAL LN (LN2)	NUMBER EXAMINED:	32 20 14 36	37 19 23 44	
TESTIS (TR)	NUMBER EXAMINED:	37 18 15 44	47 21 20 47	
SPLEEN (SP)	NUMBER EXAMINED:	50 28 23 50	49 29 26 50	
BONE STERNUM (BN1)	NUMBER EXAMINED:	49 24 22 49	50 25 24 50	
BONE FEMUR/JOINT (BN2)	NUMBER EXAMINED:	50 25 22 48	50 25 24 50	
MARROW STERNUM (BN1)	NUMBER EXAMINED:	48 24 22 50	50 25 24 50	
MARROW FEMUR (BN2)	NUMBER EXAMINED:	50 25 22 47	50 25 24 50	
ESOPHAGUS (ES)	NUMBER EXAMINED:	49 25 22 50	50 25 24 50	
LIVER (LI)	NUMBER EXAMINED:	50 50 50 50	49 32 30 50	
..B-HEPATOCELLULAR ADENOMA		3 3 4 10	1 2 1 0	
..N-HEPATOCELLULAR CARCINOMA		4 2 5 8	0 0 0 1	
..B-HEMANGIOSARCOMA		1 1 1 0	3 0 1 0	
..B-HEMANGIOMA		0 2 0 0	0 2 0 0	
GALLBLADDER (GB)	NUMBER EXAMINED:	43 29 44 41	41 22 15 45	

Table 6 (continued)

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PRINTED: 04-JAN-80
PAGE: 3

STUDY NUMBER: 852939

*** PATH/TOX SYSTEM OUTPUT ***
AN EIGHTEEN MONTH CARCINOGENICITY FEEDING STUDY
IN MICE WITH ORB 3770
INCIDENCE SUMMARY

ORGAN AND FINDING DESCRIPTION	NUMBER OF ANIMALS AFFECTED					
	MALE		FEMALE		TOTAL	
SEX: GROUP: 1-2-3-4	1	2	3	4	1	2
NUMBER: 50 50 50 50 50 50 50	50	50	50	50	50	50
ORGAN AND FINDING DESCRIPTION	1	2	3	4	1	2
BALIVARY GLANDS (SG)	50	25	22	50	49	25
STOMACH (ST)	50	25	22	50	49	25
PANCREAS (PA)	47	21	22	49	46	24
PANCREAS (PA)	50	26	22	50	49	24
ADRENAL GLANDS (AD)	0	1	0	0	0	0
ADRENAL GLANDS (AD)	47	22	20	46	44	22
ADRENAL GLANDS (AD)	0	0	1	0	0	0
ADRENAL GLANDS (AD)	44	19	20	43	42	21
ADRENAL GLANDS (AD)	46	16	21	46	46	18
ADRENAL GLANDS (AD)	48	25	22	48	46	23
ADRENAL GLANDS (AD)	50	25	22	50	47	23
ADRENAL GLANDS (AD)	50	39	29	50	50	29
ADRENAL GLANDS (AD)	50	23	22	50	48	23
ADRENAL GLANDS (AD)	50	25	24	49	0	0
ADRENAL GLANDS (AD)	0	1	1	0	0	0
ADRENAL GLANDS (AD)	50	24	24	49	0	0
ADRENAL GLANDS (AD)	50	25	22	50	0	0
ADRENAL GLANDS (AD)	50	34	30	50	0	0
ADRENAL GLANDS (AD)	0	0	0	0	49	30
ADRENAL GLANDS (AD)	0	0	0	0	0	1
ADRENAL GLANDS (AD)	0	0	0	0	49	30
ADRENAL GLANDS (AD)	0	0	0	0	0	0
ADRENAL GLANDS (AD)	0	0	0	0	0	1

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Table 6 (continued)

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PRINTED: 06-JAN-68
PAGE: 4
STUDY NUMBER: 852939

*** PATH/TOX SYSTEM OUTPUT ***
AN EIGHTEEN MONTH CARCINOGENICITY FEEDING STUDY
IN MICE WITH ORG 3770
INCIDENCE SUMMARY

... NUMBER OF ANIMALS AFFECTED ...

TABLE INCLUDES:	SEX:		MALE		FEMALE	
	GROUP	1	2	3	4	5
SEX=ALL; GROUP=ALL; SCREEN=ALL; NCES=ALL	NUMBER	50	50	50	50	50
DEATH=ALL; FIND=B,M,H; SUBSET=ALL	NUMBER EXAMINED:	0	0	0	0	0
ORGAN AND FINDING DESCRIPTION	NUMBER EXAMINED:	0	0	0	0	0
.. FROM PREVIOUS PAGE ..	NUMBER EXAMINED:	0	0	0	0	0
UTERUS (UT)	NUMBER EXAMINED:	0	0	0	0	0
--B-EPIDIDYMAL STROMAL POLY	NUMBER EXAMINED:	0	0	0	0	0
--B-RENALSTOMA	NUMBER EXAMINED:	0	0	0	0	0
PITUITARY GLAND (PG)	NUMBER EXAMINED:	49	22	21	49	24
THYROID GLAND (TG)	NUMBER EXAMINED:	48	23	22	50	46
--B-FOLLICULAR CELL ADENOMA	NUMBER EXAMINED:	0	0	1	0	0
PARATHYROID GLS. (PT)	NUMBER EXAMINED:	26	9	9	27	23
--B-ADENOMA	NUMBER EXAMINED:	0	0	0	0	0
ADRENAL GLANDS (AG)	NUMBER EXAMINED:	49	24	22	50	48
--B-W/PNECROMORPHOTOMA	NUMBER EXAMINED:	0	0	0	0	0
--B-W/CORTICAL ADENOMA	NUMBER EXAMINED:	1	0	0	0	0
ADRENAL CORTEX (AC1)	NUMBER EXAMINED:	0	0	0	0	0
ADRENAL MEDULLA (AC2)	NUMBER EXAMINED:	0	0	0	0	0
EYES (EY)	NUMBER EXAMINED:	49	31	32	50	49
MUSC BICEPS PER (BW)	NUMBER EXAMINED:	50	23	21	50	25
SKIN RING (RC1)	NUMBER EXAMINED:	50	34	32	50	27
--B-PIDIOZARCONA	NUMBER EXAMINED:	0	0	0	0	0
--B-SEBACEOUS CELL ADENOMA	NUMBER EXAMINED:	0	0	1	0	0
MAMMARY G LND (MG1)	NUMBER EXAMINED:	9	2	1	8	47
--B-CARCINOMA	NUMBER EXAMINED:	0	0	0	0	0
SPINAL CORD (SC)	NUMBER EXAMINED:	0	0	0	0	0
CAVITY (CA)	NUMBER EXAMINED:	0	0	0	0	0
SKIN (SK)	NUMBER EXAMINED:	0	0	0	0	0
GENERAL COMMENTS (GC)	NUMBER EXAMINED:	0	0	0	0	0

Table 7
Intercurrent Mortality Rates
Male Mice

<u>Weeks</u>	<u>Control</u>			<u>Low</u>			<u>Medium</u>			<u>High</u>		
	S	D	%	S	D	%	S	D	%	S	D	%
0-50	50	5	10	50	3	6	50	0	0	50	2	4
51-78	45	19	42.2	47	22	46.8	50	20	40	48	23	47.9
Term.	26			25			30			25		

Peto Test: p-value = 0.3956

Female Mice

<u>Weeks</u>	<u>Control</u>			<u>Low</u>			<u>Medium</u>			<u>High</u>		
	S	D	%	S	D	%	S	D	%	S	D	%
0-50	50	3	6	50	2	4	50	4	8	50	1	2
51-78	47	20	42.5	48	23	47.9	46	20	43.5	49	21	42.9
Term.	27			25			26			28		

Peto Test: p-value = 0.2613

Notes: S: Number of animals starting during the period
D: Deaths
%: Percent of death during the period

Table 8

Summary of Mean Body Weight(g) with (Standard Deviation)

The Male Mice Study

Dose	Week 1	Week 77	Gain in Wt.	Gain rel. to Control
Control	30.7 (2)	42.5 (4.1)	11.8	-
Low	30.5 (1.7)	42.7 (5.5)	12.2	3.38%
Medium	30.3 (2.0)	42.2 (4.8)	11.9	0.84%
High	29.6 (2.1)	39.8 (3.2)	10.2	-13.55%

Table 9

Summary of Mean Body Weight(g) with (Standard Deviation)

The Female Mice Study

Dose	Week 1	Week 77	Gain in Wt.	Gain rel. to Control
Control	24.8 (1.3)	38 (3.6)	13.2	-
Low	24.4 (1.4)	37.2 (3.9)	12.8	-3.03%
Medium	25 (1.8)	37.7 (3.8)	12.7	-3.78%
High	24.5 (1.5)	36.4 (3.2)	11.9	-9.84%

Note: A negative sign stands for decrease in weight gain relative to control.

Sparenborg
HFD-120

Statistical Review and Evaluation
(An Addendum)

NDA #: 20-415

Date: SEP -6 1995

Applicant: Organon Inc.

SECTION

Name of Drug: Remeron (Mirtazapine) Tablets

SEP 6 1995

Documents Reviewed:

1. NDA submission volumes 2.27 to 2.31 "An Eighteen Month Carcinogenicity Feeding Study in Mice With ORG 3770", March 13, 1989, Date of Documents, Jan. 30, 1995.
2. NDA submission volumes 2.32 to 2.36 "A Twenty-Four Month Feeding Study in Rats With ORG 3770", May 11, 1990, Date of Documents, Jan. 30, 1995.
3. NDA original amendments, Data diskettes and computer listings of Carcinogenicity studies, Date of Document, May 3, 1995.

I. Background

The two animal carcinogenicity studies (one in rats and one in mice) included in this NDA submission have been reviewed by the Division of Biometrics. A statistical review and evaluation report was issued on June 30, 1995. In the previous review, our analyses showed significant positive linear trends in the thyroid gland follicular cell adenoma/cystadenoma (age-adjusted: $p = 0.0153$; age-unadjusted: $p = 0.0045$) in male rats and in liver hepatocellular adenoma (age-adjusted: $p = 0.008$) in female rats. Dr. Steve Sparenborg, HFD-120, who is the reviewing pharmacologist of this NDA has requested the Division of Biometrics to perform trend test on liver hepatocellular adenoma and carcinoma combined in rats and mice, and on thyroid gland follicular cell combined adenoma/cystadenoma/carcinoma in rats. The purpose of this addendum is to report the results of the analyses when trend tests were performed on the above combined tumors.

II. The Rat Study

The methods described in the paper of Peto et al. ("Guidelines for Simple, Sensitive Significance Tests for Carcinogenic Effects in Long-Term Animal Experiments", In Long-Term and Short-Term Screening Assays for Carcinogens: A Critical Appraisal, International Agency for Research on Cancer Monographs, Annex to Supplement 2, World Health Organization, 311-426, 1980) and the methods of exact permutation trend test were used to test the linear trend in the liver hepatocellular adenoma and carcinoma combined, and thyroid gland follicular cell adenoma/cystadenoma/carcinoma combined in both sexes. The time intervals 0-50, 51-80, and 81-105 weeks were used in the analyses. The actual dose levels 0, 2, 20, and 60 mg/kg/day were the scores assigned to the control, low, medium, and high dose

groups, respectively. As mentioned in the previous review, the age-adjusted method was applied only to the tissues with all of the animals or more than 98% of animals examined microscopically. The age-unadjusted method was applied to the tumor which the age-adjusted method can not be applied. The results of the above analyses showed that there was a significant (at 0.005 level for a common tumor, and at 0.025 level for a rare tumor) positive linear trend in the thyroid gland follicular cell combined adenoma/cystadenoma/carcinoma (age-adjusted: $p = 0.0047$; age-unadjusted: $p = 0.0006$) in male rats.

The incidence rates of the tested tumors are listed as follows:

Tumor/organ	Incidence of Tumors				P-values	
					Unadjusted	adjusted
Males:						
Liver:						
Hepatocellular Adenoma and Carcinoma						
	(50)	(50)	(50)	(50)		
	1	1	1	6		0.0101
Thyroid Gland:						
Follicular Cell Adenoma/Cystadenoma/carcinoma						
	(48)	(49)	(50)	(46)		
	1	5	6	12	0.0006*	0.0047*
Females:						
Liver:						
Hepatocellular Adenoma and Carcinoma						
	(50)	(50)	(50)	(50)		
	1	0	4	6		0.0077
Thyroid Gland:						
Follicular Cell Adenoma/Cystadenoma/carcinoma						
	(50)	(49)	(50)	(50)		
	1	1	2	1	0.5571	0.4887

Noted that in order to reduce the overall false positive rate, the following decision rule was used to adjust the effect of multiple testings. A positive linear trend is considered not to occur by chance of variation alone if the p-value is less than 0.005 for a common tumor, and 0.025 for a rare tumor.

The pairwise comparison between the high dose and control groups was performed on the thyroid gland follicular cell combined adenoma/cystadenoma/carcinoma in male rats. The results showed that there is a significantly higher incidence rates in the high dose vs control groups ($p = 0.0107$).

Noted that in this review, the data included in the sponsor's submitted computer diskettes were used for the analyses.

III. The Mouse Study

The methods described in Peto et al. (1980) and the methods of exact permutation trend test were used to test the linear trend in the liver hepatocellular adenoma and carcinoma combined in both sexes. The time intervals 0-50 and 51-78 weeks were used in the analyses. The actual dose levels 0, 2, 20, and 200 mg/kg/day were the scores assigned to the control, low, medium, and high dose groups, respectively. The results of the above analyses showed that there was a significant (at 0.005 level for a common tumor, and at 0.025 level for a rare tumor) positive linear trend in the liver hepatocellular adenoma and carcinoma combined (age-adjusted: $p = 0.0015$) in males.

The incidence rates of the tested tumors are listed as follows:

<u>Tumor/organ</u>	<u>Incidence of Tumors</u>				<u>P-values</u>	
					<u>Unadjusted</u>	<u>adjusted</u>
Males:						
Liver:						
Hepatocellular Adenoma and Carcinoma						
	(50)	(50)	(50)	(50)		
	7	5	11	17		0.0015*
Females:						
Liver:						
Hepatocellular Adenoma and Carcinoma						
	(50)	(50)	(50)	(50)		
	1	2	1	1		0.4327

The pairwise comparison between the high dose and control groups was performed on the liver hepatocellular adenoma and carcinoma combined in males. The results of the analyses showed that there is a significantly (at 0.05 level) higher incidence rates in the high dose vs control groups ($p = 0.0198$).

Noted that there is a discrepancy in the incidence rates of the high dose males in the liver hepatocellular adenoma and carcinoma combined between the sponsor's and the reviewer's analyses. Male mice number 4010 in high dose group has both liver hepatocellular adenoma and hepatocellular carcinoma, hence, this animal was counted as one in the above reviewer's analysis. It seems that the sponsor did not consider this duplicate situation which caused the incidence rate of combined hepatocellular adenoma/carcinoma in high dose males to be 18

instead of 17. Appendix 1 (the sponsor's Appendix F in Volume 2.27) showed the percentage of livers with adenomas and carcinomas and the sponsor's analysis results. The incidence rates of hepatocellular adenoma/carcinoma are 7, 5, 11, and 18 in control, low, medium, and high dose groups, respectively.

IV. Summary

The results of the trend test showed that there were significant positive linear trends in the thyroid gland follicular cell combined adenoma/cystadenoma/carcinoma (age-adjusted: $p = 0.0047$; age-unadjusted: $p = 0.0006$) in male rats and in the liver hepatocellular adenoma and carcinoma combined (age-adjusted: $p = 0.0015$) in male mice.

Noted that in order to reduce the overall false positive rate associated with in the trend test, the following decision rule was used to adjust the effect of multiple testings. A positive linear trend is considered not to occur by chance of variation alone if the p-value is less than 0.005 for a common tumor, and 0.025 for a rare tumor.

The pairwise comparisons between the high dose and control groups were performed on the tumors with statistically significant trend tests. The results showed that there are significantly (at 0.05 level) higher incidence rates in the high dose vs control groups in thyroid gland follicular cell combined adenoma/cystadenoma/carcinoma in male rats ($p = 0.0107$) and in liver hepatocellular adenoma and carcinoma combined in male mice ($p = 0.0198$).

Daphne Lin

Daphne Lin, Ph.D.
Mathematical Statistician

Concur:

Karl K. Lin 9/6/95
Karl K. Lin, Ph.D., Group Leader, SARB

cc: Original NDA 20-415

HFD-120/Dr. Leber

HFD-120/Dr. Fitzgerald

HFD-120/Dr. Sparenborg

HFD-120/Mr. P. David

HFD-710/Chron

HFD-715/Dr. Karl Lin

HFD-715/Dr. Daphne Lin

HFD-715/Chron (SARB)

HFD-502/Assistant Director (Pharmacology)

HFD-715/DRU 2.1.1, Remeron, Organon Inc.

Appendix 1

-9-

F-9
85-2939

An Eighteen Month Carcinogenicity Feeding Study
in Mice with Org 3770
Pathology Report

RESULTS AND DISCUSSION (cont.)

Figure 3

. Percentages of Livers with Adenomas and Carcinomas

Sex	Male				Female			
Groups	I	II	III	IV	I	II	III	IV
# of livers examined	50	50	50	50	50	50	50	50
# of livers with adenomas (%)	3 6.0	3 6.0	6 12.0	10 20.0	1 2.0	2 6.2	1 3.3	0
# of livers with carcinomas (%)	4 8.0	2 4.0	5 10.0	8 16.0	0	0	0	1 2.0
combined adenomas/carcinomas (%)	7 14.0	5 10.0	11 22.0	18 36.0*	1 2.0	2 6.2	1 3.3	1 2.0

* statistically significant difference (p. <0.05)

The mouse liver has an increased sensitivity for developing primary tumors under certain experimental conditions. It is also very sensitive to compounds that have an effect on the hepatic microsomal enzyme system. In a separate study (Org 178-SDGRR 2236) a comparison of Org 3770 to a known positive enzyme inducer (phenobarbitone) was made. Org 3770 induced a definite increase in the activity of cytochrome P-450, aminopyrine-N-demethylase, aniline hydroxylase, Ethoxycoumarin-O-deethylase and glutathionine-S-transferase in male mouse livers.

0101

DAVID

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS
REVIEW OF CHEMISTRY AND MANUFACTURING CONTROLS

NDA 20,415

	<u>letterdate</u>	<u>stampdate</u>	<u>rec'd by chemist</u>	<u>COMPLETED</u>
INITIAL SUBMISSION:	26-JAN-95	30-JAN-95	30-JAN-95	5-MAY-95
AMENDMENTS:	21-DEC-94	22-DEC-94	22-DEC-94	5-MAY-95
	13-FEB-95	14-FEB-95	14-FEB-95	5-MAY-95
	27-FEB-95	28-FEB-95	03-MAR-95	5-MAY-95

CHEMIST REVIEW: # 1 **SPONSOR:** ORGANON

REVIEW CHEMIST: M.Zarifa, Ph.D **ADDRESS:** 375 Mt. Pleasant Avenue
West Orange, NJ 07052

PRODUCT NAME:

Proprietary: REMERON
USAN: Mirtazapine
Code Name/Number: **ORG 3770**

MAY 30 1995

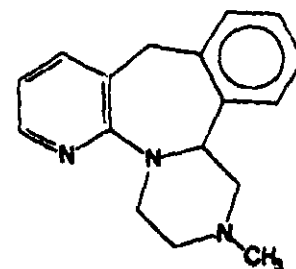
DOSAGE FORM/ROUTE OF ADMINISTRATION: 15 mg and 30 mg Tablets/Oral

PHARMACOL.CATEGORY/PRINCIPAL INDICATION: Depression

STRUCTURAL FORMULA & CHEMICAL NAME:

C₁₇H₁₉N₃ Mol. Wt. 265.36

1,2,3,4,10,14b-hexahydro-2-methylpyrazino[2,1-a]pyrido[2,3-c]benzazepine



REMARKS: The n.d.s. is a tetracyclic weak base and is insoluble in water. The n.d.s. contains a chiral center but is manufactured and controlled as the racemate. The drug product batches showed good dissolution (NLT in 20 min). The sponsor proposes a 48-months expiry date but has no stability data to support it. Other CMC deficiencies also exist in the NDA that need to be addressed by the sponsor.

CONCLUSIONS & RECOMMENDATIONS: RECOMMEND THAT NDA 20-415 FOR ORG 3770 TABLETS IS NOT APPROVABLE. SATISFACTORY CORRECTION OF CMC DEFICIENCIES IS REQUIRED. SEE CMC DEFICIENCY LETTER.

cc: ORIG: NDA
HFD-120/Div. File
HFD-120/CSO/P.David
HFD-120/SBlum/MZarifa
INIT:

AMB
5/23/95

filename: N020415.000

Mona Zarifa
Mona Zarifa, Ph.D., Chemist

NDA 20,415

ORG 3770

ORGANON

2

SUPPORTING DOCUMENTS:

Original NDA submission dated April 29, 1994.

N.D.S.

Drug product

HDPE resin/bottles

(Drug Plastic & Glass)

Closures/ innerseal/resin

Colorant

Blister packs/backing

(Reynolds);

RELATED DOCUMENTS: IND

CONSULTS: Environmental Assessment [Dr. Vincent] -- sent January 30, 1995
Inspection Request -- sent March 9, 1995

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS
REVIEW OF CHEMISTRY AND MANUFACTURING CONTROLS

NDA 20,415

	<u>letterdate</u>	<u>stampdate</u>	<u>rec'd by chemist</u>	<u>COMPLETED</u>
INITIAL SUBMISSION:	26-JAN-95	30-JAN-95	30-JAN-95	5-MAY-95
AMENDMENTS:	21-DEC-94	22-DEC-94	22-DEC-94	5-MAY-95
	13-FEB-95	14-FEB-95	14-FEB-95	5-MAY-95
	27-FEB-95	28-FEB-95	03-MAR-95	5-MAY-95
	25-MAY-95	30-MAY-95	31-MAY-95	14-JUN-95

CHEMIST REVIEW: # 2

SPONSOR: ORGANON

REVIEW CHEMIST: M.Zarifa, Ph.D

ADDRESS: 375 Mt. Pleasant Avenue
West Orange, NJ 07052

PRODUCT NAME:

Proprietary:

REMERON

USAN:

Mirtazapine

Code Name/Number:

ORG 3770

JUN 20 1995

DOSAGE FORM/ROUTE OF ADMINISTRATION: 15 mg and 30 mg Tablets/Oral

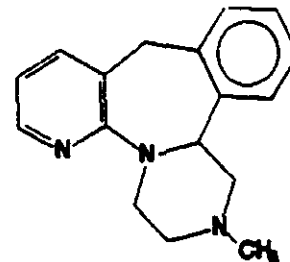
PHARMACOL.CATEGORY/PRINCIPAL INDICATION: Depression

STRUCTURAL FORMULA & CHEMICAL NAME:

$C_{17}H_{19}N_3$

Mol. Wt. 265.36

1,2,3,4,10,14b-hexahydro-2-methylpyrazino[2,1-a]pyrido[2,3-c]benzazepine



REMARKS: In the May 25, 1995 amendment the sponsor provides updated test methods for the n.d.s. specifications, validation data for the new assay, and modifications for the drug product manufacturing process and release/stability specifications.

CONCLUSIONS & RECOMMENDATIONS: RECOMMEND THAT NDA 20-415 FOR ORG 3770 TABLETS IS NOT APPROVABLE. SATISFACTORY CORRECTION OF CMC DEFICIENCIES IS REQUIRED. SEE CMC DEFICIENCY LETTER.

cc: ORIG: NDA
HFD-120/Div. File
HFD-120/CSO/P.David
HFD-120/SBlum/MZarifa
INIT: *AMB 6/19/95*

filename: N020415.001

Mona Zarifa
Mona Zarifa, Ph.D., Chemist

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS
REVIEW OF CHEMISTRY AND MANUFACTURING CONTROLS

NDA 20,415

	<u>letterdate</u>	<u>stampdate</u>	<u>rec'd by chemist</u>	<u>COMPLETED</u>
INITIAL SUBMISSION:	26-JAN-95	30-JAN-95	30-JAN-95	5-MAY-95
AMENDMENT:	10-AUG-95	11-AUG-95	12-AUG-95	28-MAY-95

CHEMIST REVIEW: # 3

SPONSOR: ORGANON

REVIEW CHEMIST: M.Zarifa, Ph.D

**ADDRESS: 375 Mt. Pleasant Avenue
West Orange, NJ 07052**

PRODUCT NAME:

Proprietary:

REMERON

USAN:

Mirtazapine

Code Name/Number:

ORG 3770

SEP 28 1995

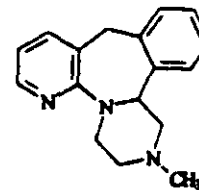
DOSAGE FORM/ROUTE OF ADMINISTRATION: 15 mg and 30 mg Tablets/Oral

PHARMACOL.CATEGORY/PRINCIPAL INDICATION: Depression

STRUCTURAL FORMULA & CHEMICAL NAME:

C₁₇H₁₉N₃

Mol. Wt. 265.36



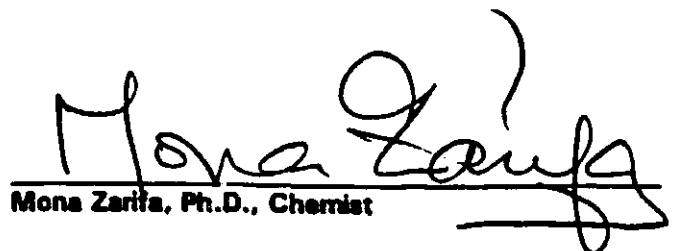
1,2,3,4,10,14b-hexahydro-2-methylpyrazino[2,1-s]pyrido[2,3-c]benzazepine

**REMARKS: In this amendment the sponsor responds to the two deficiency letters
The data provided are adequate and satisfactory.**

**CONCLUSIONS & RECOMMENDATIONS: CORRECTION OF CMC DEFICIENCIES HAS BEEN DONE.
RECOMMEND THAT NDA 20-415 FOR ORG 3770 TABLETS IS APPROVABLE AND APPROVED
CONTINGENT UPON RECEIPT OF APPROVABLE RECOMMENDATION FROM COMPLIANCE AND
FROM EA REPORT. RECOMMEND RESTRICTION OF EXPIRY DATE TO 24 MONTHS AT THIS TIME.**

cc: ORIG: NDA
HFD-120/Div. File
HFD-120/CSO/P.David
HFD-120/SBlum/MZarifa
INIT:

filename: N020415.001


Mona Zarifa, Ph.D., Chemist



ENVIRONMENTAL ASSESSMENT
AND
FINDING OF NO SIGNIFICANT IMPACT
FOR

Remeron™
(mirtazapine)

**REDACTIONS MADE
BY APPLICANT**

Tablets 15mg/30mg

NDA 20-415

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

**Division of Neuropharmacological Drug
Products HFD-120**

FINDING OF NO SIGNIFICANT IMPACT

NDA 20-415

Remeron™

(mirtazapine)

Tablets 15mg/30mg

The National Environmental Policy Act of 1969 (NEPA) requires all Federal agencies to assess the environmental impact of their actions. FDA is required under NEPA to consider the environmental impact of approving certain drug product applications as an integral part of its regulatory process.

The Food and Drug Administration, Center for Drug Evaluation and Research has carefully considered the potential environmental impact of this action and has concluded that this action will not have a significant effect on the quality of the human environment and that an environmental impact statement therefore will not be prepared.

In support of their new drug application for Remeron™, Organon Inc. has conducted a number of environmental studies and prepared an environmental assessment in accordance with 21 CFR 25.31a(a) (attached) which evaluates the potential environmental impacts of the manufacture, use and disposal of the product.

Mirtazapine is a chemically synthesized drug which is administered as a 15mg/30mg tablet in the treatment of Major Depressive Disorders. The drug substance is manufactured by Diosynth B.V. in The Netherlands. The drug products are produced by N.V. Organon in The Netherlands. Packaging, testing and distribution of the drug product in the United States is performed by Organon Inc. with some packaging performed by ~~in the United States~~. The finished drug product will be used in hospitals, clinics and private homes throughout the United States.

Drug substance that is introduced into the patient is extensively metabolized, but residual mirtazapine and metabolites will be excreted in the urine and feces and distributed into wastewater treatment systems throughout the United States. Chemical and physical test results indicate that mirtazapine will most likely be restricted to the aquatic and terrestrial environments. Mirtazapine significantly sorbs to soils and may be transported from the aquatic environment to the terrestrial environment. Mirtazapine rapidly photodegrades and is an important mechanism of degradation.

As mirtazapine is expected to persist in the aquatic and terrestrial environments for some time, the toxicity of mirtazapine to several environmental organisms was characterized. The lowest reported effect concentration was ca. 0.5 ppm for growth of parent *Daphnia magna*, a water flea, in a chronic toxicity test. The maximum expected environmental concentration is several orders

of magnitude lower than this toxicity value and therefore no adverse environmental impacts are expected.

Disposal of the drug may result from out of specification lots, discarding of unused or expired product, and user disposal of empty or partly used product and packaging. Returned or out-of-specification drug substance and rejected or returned drug product will be disposed of at a licensed landfill. At U.S. hospitals and clinics, empty or partially empty packages will be disposed according to hospital/clinic regulations. From home use, empty or partially empty containers will typically be disposed of by a community's solid waste management system which may include landfills, incineration and recycling, while minimal quantities of unused drug may be disposed of in the sewer system. For manufacture of the drug substance, the firm has provided letters from the Dutch governmental authorities that they are in compliance with the laws of The Netherlands.

The Center for Drug Evaluation and Research has concluded that the product can be manufactured, used and disposed of without any expected adverse environmental effects. Precautions taken at the sites of manufacture of the bulk product and its final formulation are expected to minimize occupational exposures and environmental release. Adverse effects are not anticipated upon endangered or threatened species or upon property listed in or eligible for listing in the National Register of Historic Places.

11/22/95
DATE

P. G. Vincent

APPROVED

P. G. Vincent, Ph.D.
Environmental Scientist
Center for Drug Evaluation and Research

11/29/95
DATE

Nancy B. Sager

CONCURRED

Nancy Sager
Environmental Scientist
Center for Drug Evaluation and Research

Attachments: Environmental Assessment
Material Safety Data Sheet (drug substance)

Project: REMERON™
Document No.: PDR-211.03

ORGANON INC.
West Orange, New Jersey 07052

**REDACTIONS MADE
BY APPLICANT**

**ENVIRONMENTAL IMPACT ASSESSMENT REPORT
FOR REMERON™**

REVISION 03

Pharmaceutical Development Department
Product Development and Government Affairs
October 30, 1995

**ENVIRONMENTAL IMPACT ASSESSMENT REPORT
FOR REMERON™ - REVISION 03**

**REDACTIONS MADE
BY APPLICANT**

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REDACTIONS MADE
BY APPLICANT**ENVIRONMENTAL IMPACT ASSESSMENT REPORT
FOR REMERON™ - REVISION 03****Table of Contents (continued)**

APPENDIX A:	Compliance Documentation from the Dutch Government
APPENDIX B:	Material Safety Data Sheets (MSDS) for the Excipients Used in the Manufacture of Remeron™ Tablets
CONFIDENTIAL APPENDIX I:	Information on the Impurities of Mirtazapine
CONFIDENTIAL APPENDIX II:	Process Flow Diagram for the Synthesis of Mirtazapine Drug Substance
CONFIDENTIAL APPENDIX III:	Process Flow Diagram for the Manufacture of Remeron™ Tablets
CONFIDENTIAL APPENDIX IV:	SDGRR-2290, "Biotransformation of ORG 3770 in Man and Laboratory Animals"
CONFIDENTIAL APPENDIX V:	Percent of Metabolites of Mirtazapine in Urine
CONFIDENTIAL APPENDIX VI:	RDGA-306, "Material Disposal" RDGA-533, "Handling and Disposal of Hazardous Waste Solvents"

**ENVIRONMENTAL IMPACT ASSESSMENT REPORT
FOR REMERON™ - REVISION 03**

**REDACTIONS MADE
BY APPLICANT**

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CONFIDENTIAL APPENDIX VII:	Market Projections and MEEC Calculation for Remeron™ Tablets
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	A. Index
	B. Summary of Test Results
	C. Test Reports
CONFIDENTIAL APPENDIX IX:	Preclinical Toxicology Data on Mirtazapine

REDUCTIONS MADE
BY APPLICANT

1. **Date:** October 30, 1995
2. **Name of Applicant:** Organon Inc.
3. **Address:** 375 Mt. Pleasant Avenue
West Orange, New Jersey 07052
4. **Description of Proposed Action:**

4.1 Requested Approval

In accordance with 21 CFR 25.31(a) for Environmental Assessment, Organon Inc. is requesting approval to package, distribute and sell Remeron™ (mirtazapine) 15 mg and 30 mg tablets (NDA No. 20-415) for the treatment of Major Depressive Disorders.

4.2 Need for Action

Several classes of antidepressants (i.e., tricyclics, heterocyclics, selective serotonin reuptake inhibitors and monoamine oxidase inhibitors) and several compounds within each class, which are on the market, are effective and safe choices for the pharmacological treatment of many patients with a diagnosis of Major Depressive Disorders. Nevertheless, despite the large number of drugs that are available for the treatment of depression, there remain many patients with this disease who are not responsive and/or cannot tolerate treatment with these available medications.

Remeron™ (mirtazapine), a member of the novel piperazinoazepine class of compounds, is a weakly basic tetracyclic, centrally active presynaptic α_2 -antagonist, which modulates central serotonin function via an interaction with 5-HT₂ and 5-HT₃ receptors. It also possesses antihistaminic and weak α_1 -adrenolytic properties. Clinical studies have shown that Remeron™ is effective and safe for the treatment of Major Depressive Disorders. Remeron™ was also shown to reduce anxiety, often associated with depressive disorders, improve sleep and reduce suicidal thought and ideation. Mirtazapine lacks the anticholinergic effects associated with the tricyclic antidepressants and it does not induce agitation or gastrointestinal distress, which are side effects associated with the selective serotonin reuptake inhibitors.

4.3 Location Where the Product is Produced**4.3.1 The Netherlands (Drug Substance and Drug Product Manufacturing)**

The drug substance, mirtazapine, is produced by:

The drug product, Remeron™ (mirtazapine) 15 mg or 30 mg tablets, are produced by:

N.V. Organon
Molenstraat 110
5340 BH Oss
The Netherlands

4.3.2 The United States (Packaging, Testing and Distribution)

Remeron™ (mirtazapine) 15 mg and 30 mg tablets are packaged in HDPE bottles and labeled by:

Organon Inc.
6350 Hedgewood Drive
Allentown, Pennsylvania 18105

Remeron™ (mirtazapine) 15 mg and 30 mg tablets are packaged in PVC blisters and labeled by:

Remeron™ (mirtazapine) 15 mg and 30 mg tablets are quality control tested by:

Organon Inc.
375 Mount Pleasant Avenue
West Orange, New Jersey 07052

4.4 Locations Where the Product Will be Used and Disposed Of

4.4.1 Use of Drug Product

The use of the drug product, Remeron™ (mirtazapine) tablets, is limited to patients being treated for Major Depressive Disorders. Treatment will occur in patients in hospitals, clinics and private homes throughout the United States. Its use is not expected to be more prevalent in any particular geographic area.

4.4.2 Disposal of Drug Substance and Drug Product in The Netherlands

Waste resulting from manufacturing and testing of the active ingredient, mirtazapine and the finished product, Remeron™ (mirtazapine) tablets, or from rejected or outdated drug substance or finished product will be disposed of by

All waste is disposed of in accord with applicable regulations and current letters of compliance with these licenses are provided in APPENDIX A.

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4.4.3 Disposal of Drug Product in the United States

Returned and rejected product, packaging and testing waste containing the active drug are delivered to Organon, Inc, West Orange, NJ, 07052.

These crushed wastes are transported by:

For delivery to:

Managed by:

and delivered to a landfill.

4.4.4 Waste Packaging Materials

Waste bottle-packaging materials, generated by Organon Inc., Allentown, Pennsylvania, are recycled (paper) or disposed of by landfill by the local waste removal company. The current waste disposal firms for the Allentown, Pennsylvania facility are:

Berger Sanitation
P.O. Box 1412
Bethlehem, Pennsylvania 18018-1412

Cogle's Recycling Inc.
1000 South Fourth Street
Hamburg, Pennsylvania 19526

4.5 Types of Environments Present At and Adjacent to Production Sites

4.5.1 The Netherlands

I. Manufacturing Sites

N.V. Organon are located in Oss, The Netherlands, a town of approximately 50,000 inhabitants. The factories are located on a 160,000 square meter site together with other properties of AKZO Nobel, including research and development laboratories, technical service offices, control laboratories etc. The site borders a meat canning company, a railway station, a housing development and administrative offices. The region is flat and the climate is temperate. The region is not a flood or earthquake area.

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ii. Disposal Sites

Environments surrounding the disposal facilities are typical of waste disposal sites as regulated by the applicable governing body. Letters of reference, stating compliance with applicable regulations are provided in APPENDIX A.

4.5.2 The United States

I. Packaging and Labeling Site, Organon Inc.

The building at 6350 Hedgewood Drive, Allentown, Pennsylvania is located within an industrial park comprised of approximately 8.64 acres of land. The packaging warehouse contains space for storage of materials, equipment for packaging of pharmaceuticals, and a packaging station. A warehouse from which released packaged material is distributed is also located at this facility, with storage and general office space for distribution personnel. The region is hilly and the climate is temperate.

iii. Testing Site, Organon Inc.

The quality control testing laboratory at West Orange, New Jersey is located in a suburban area. The facility is situated on property bordering an electric utilities substation, a private golf course, an electric switching station, an office building and condominiums. The region is hilly and the climate is temperate.

iv. Disposal Sites

Environments surrounding the disposal facilities are typical of waste disposal sites as regulated by the United States governing bodies, i.e. Environmental Protection Agency.

5. Identification of Chemical Substances that are Subject to the Proposed Action:

5.1 Drug Substance

5.1.1 Names:

United States Adopted
Name (USAN): Mirtazapine

CAS Registry Number: 85650-52-8

Laboratory Code Name: ORG 3770

Trade Name: Remeron™

Chemical Names:

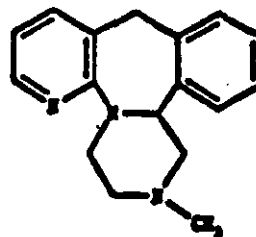
- (1) pyrazino [2,1-a]pyrido[2,3-c][2]
benzazepine, 1,2,3,4,10,14b-
hexahydro-2-methyl-
- (2) 1,2,3,4,10,14b-hexahydro-2-methyl-
pyrazino[2,1-a]pyrido[2,3-c]
benzazepine

5.1.2 Physical and Chemical Characteristics:

Molecular Formula: $C_{17}H_{19}N_3$

Molecular Mass: 265.36

Structural Formula:



Appearance: White to creamy white crystalline powder

Melting Point: 120°C-124°C

Solubility:

n-Hexane:	10 mg/mL
Toluene:	150 mg/mL
Methanol:	350 mg/mL
Diethylether:	35 mg/mL
Water:	Practically insoluble

5.1.3 Impurities

The total level of impurities present in mirtazapine is not more than 0.5%. The chemical names and structures of the impurities are presented in CONFIDENTIAL APPENDIX I.

A process flow diagram for the synthesis of mirtazapine is provided in CONFIDENTIAL APPENDIX II. The material safety data sheet for mirtazapine is provided in APPENDIX B.

5.2 Excipients:

For tablet production:

For coating of the tablets:

A process flow diagram for the manufacture of Remeron™ tablets, presented in CONFIDENTIAL APPENDIX III, provides information on the tablet components and the type of equipment used to manufacture the drug product. Material safety data sheets for each excipient are included in APPENDIX B.

5.3 Metabolites

Mirtazapine is extensively metabolized and quantitatively eliminated in urine (75%) and in feces (15%), following ingestion by patients. Thus, metabolites are expected to enter the environment. The biotransformation pathways are presented on page 32 of SDGRR 2290, "Biotransformation of ORG 3770 in Man and Laboratory Animals" provided in CONFIDENTIAL APPENDIX IV. The major excreted metabolites, 8-hydroxy- ORG 3770-glucuronide (10% to 30%) and quaternary-N-glucuronide (10% to 20%) are not pharmacologically active. The relative percentage of these and all other metabolites found in the urine 24 hours after administration of mirtazapine are summarized in CONFIDENTIAL APPENDIX V.

6. Introduction of Substances into the Environment:

The manufacture of the active ingredient, mirtazapine, and the drug product, Remeron™ (mirtazapine) 15 mg and 30 mg tablets, will be carried out by and N.V. Organon, Oss, The Netherlands, respectively. Therefore, no environmental release resultant to these operations will occur in the United States.

Packaging, labeling and distribution for commercialization in the United States is done at three different sites in New Jersey and waste generated from these operations are expected to be minimal.

6.1 Introduction of Substances into the Environment in The Netherlands

6.1.1 Substances Expected to be Emitted

Facilities located in The Netherlands (N.V. Organon) are monitored from an environmental point of view by the local and national governments. Both facilities operate in compliance with environmental permits from the Province of North Brabant and the Water Board "De Maaskant" (see APPENDIX A) and with national and local regulations concerning waste water discharge and waste treatment.

Three distinct types of wastes can be generated from these facilities: solid waste, liquid waste and air emission.

Solid waste consists of non-hazardous materials (paper, shipping materials), and pharmaceutical solids which result from weighing dry powder chemicals, and processing these chemicals into basic or active granulates and solids.

Liquid wastes consist of water which may contain pharmaceutical waste such as hydrocarbon solvents, or water that had been used for production or cleaning purposes.

Air emissions that occur may contain manufacturing solvents. Normal emissions from the heating and use of the building occur during packaging and labeling processes for shipment to the United States for further packaging and distribution.

6.1.2 Controls Exercised

Solid waste material from the tablet manufacturing process, such as results from the weighing of dry powder chemicals and the processing of these chemicals into the basic and active granulates and solid material from the equipment and room cleaning processes, are packed appropriately and transported to an off-site regional incineration company. For the preparation of the basic and active granulates, an enclosed mixer granulator is used to prevent the emission of potentially harmful dust particles into the production area. The fluid-bed dryer is equipped with a highly efficient filter system to prevent the escape of harmful dust particles. The handling of the basic and active granulates is done in closed transport containers with closed couplings.

General measures to prevent or minimize the release of chemical residues after production consist of wet-cleaning the entire manufacturing area. Any residue material is cleaned immediately. All processing equipment is initially vacuum cleaned by the user through the dust suction system, then cleaned. All mobile machines are cleaned with copious amounts of hot water or if needed, with ethanol or acetone.

Water which may contain pharmaceutical waste from the production or the cleaning process, is cooled and pretreated according to regional permits, and in accordance with the Pollution of Surface Waters Act of the Netherlands, is discharged to a waste water treatment company. The applicable letters of compliance may be found in APPENDIX A.

The air emission from the production area to the surrounding environment is regulated by the National Nuisance Act in The Netherlands. General measures to prevent or minimize the release of airborne particles and/or vapors into the occupational and atmospheric environments during manufacturing consist of separated, well ventilated weighing rooms and production areas with sub-atmospheric pressure. Weighing equipment has local dust suction systems. Incoming air is filtered initially by Viledon F45 and subsequently by Trox T748 filters. It is conditioned at a temperature of 20°C to 22°C and a relative humidity of about 50%. Before leaving the production area, the air is filtered by a rolfilter type Froxomat F1006-20A00 and further by Trox F746 envelope filters. The number of air changes is 15 to 20 times per hour and no recirculation of air takes place.

6.1.3 Citation of, and Statement of Compliance with Applicable Emission Requirements at the Federal, State and Local Levels

Solid emissions from the manufacturing area to the environment are in compliance with the Environmental Act in the Netherlands. Liquid emissions from the manufacturing area to the environment are in compliance with the Pollution of Surface Waters Act in the Netherlands. Air emissions from the manufacturing area to the environment are in compliance with the National Nuisance Act in the Netherlands. The applicable letters of compliance are provided in APPENDIX A.

6.1.4 Effect of Approval on Compliance with Current Emissions Requirements at the Production Site

Letters from the Dutch Government certifying compliance with the applicable laws may be found in APPENDIX A. Based upon the controls described above (treatment of emitted substances by solid waste controls, waste water controls, air emission controls), the proposed action is not expected to have any significant impact on emissions produced by the existing facility, and is not expected to violate the current permit.

6.2 Introduction of Substances into the Environment in The United States

6.2.1 Substances Expected to be Emitted

Facilities located in the United States (Organon Inc., West Orange, New Jersey and Allentown, Pennsylvania,) are monitored from an environmental point of view by local and national government and operate in compliance with environmental laws from the Environmental Protection Agency, the New Jersey Department of Environment Protection and with applicable national and local regulations.

Three distinct types of wastes can be generated from these facilities, solid waste, liquid waste and air emission.

Solid waste consists of shipping and packaging materials such as cardboard shipping materials and HDPE bottles.

Liquid wastes consist of water which may contain pharmaceutical waste such as hydrocarbon solvents used in quality control testing, or water that had been used for packaging or cleaning purposes.

Air emissions that occur may contain particles of active ingredient or solvents used in quality control testing. From packaging and labeling processes, normal emissions from the heating and use of the building occur.

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Solid waste consisting of shipping and packaging materials such as cardboard shipping materials, and HDPE bottles are disposed of by recycling or landfill. Non-hazardous solid waste (paper, shipping materials) is disposed of either by recycling or by return to Organon Inc., West Orange N.J. for shredding (paper containing the Organon Logo). HDPE bottles are non-hazardous waste and are disposed of by local waste disposal authorities by burial in a landfill. Solid waste containing drug product is packaged and sent to Organon Inc, West Orange, N.J. for disposal as described in Section 4.4.3. Solid waste packaging materials generated at are close-compacted and taken by National Waste Disposal, Trenton, New Jersey for delivery to a certified landfill. PVC blister packaging materials are not incinerated.

Liquid waste from the packaging and labeling process is non-hazardous and is disposed of via the local wastewater treatment facility. Hazardous waste solvents from Quality Control testing are transferred from the source to an appropriately labeled empty safety can, which is then disposed of in accord with procedures described in RDGA-306, "Material Disposal" and RDGA-533, "Handling and Disposal of Hazardous Waste Solvents", provided in CONFIDENTIAL APPENDIX VI.

Air emissions from the packaging and labeling process are normal emissions from heating and use of the building and are non-hazardous. Laboratory hoods are available to limit particle emissions from the laboratory. A minimal level of solvents would reach the air via the laboratory hoods.

6.2.3 Citation of, and Statement of Compliance With Applicable Emission Requirements at the Federal, State and Local levels

There is no release of hazardous substances or hazardous emissions from the packaging plant at Organon Inc., Allentown, or . At Organon Inc, West Orange, New Jersey, mirtazapine has been categorized as ID 27-Dry Industrial type waste, and therefore is disposed of in accordance with New Jersey Administrative Code Regulations. Waste solvents which result from Quality Control Testing are collected in a drum and disposed of as Hazardous Waste Materials in accordance with New Jersey Administrative Code Regulations.

6.2.4 Effect of Approval on Compliance with Current Emissions Requirements at the Production Site

United States production sites will be used only for packaging, labeling, and testing of final product. Non-hazardous waste materials generated at each site will be disposed of either by recycling or by burial in a landfill. Testing solvents will be disposed of in accordance with New Jersey Department of Environmental Protection (NJDEP). The amount of waste generated by the packaging, labeling and testing of Remeron™ tablets is not expected to significantly increase the waste production at any of the sites. Therefore, the proposed action is not expected to have any impact on compliance with current waste legislation.

6.3 Estimate of Concentration of Substances Expected to Enter the Environment as a Result of Use or Disposal of Products Affected by the Action

6.3.1 Maximum Emitted Concentration (MEEC) of Mirtazapine in Wastewater from Use of Drug

The MEEC for mirtazapine, based upon the worst case scenario (that of all mirtazapine consumed by patients is excreted unmetabolized and not removed by wastewater treatment), is presented in CONFIDENTIAL APPENDIX VII. This figure is based upon a 5-year market projection using the projected maximum number of tablets that will be sold in a single year for this calculation. The MEEC is calculated to be 45.6 parts per trillion (ppt).

6.3.2 Expected Emissions from Disposal

No substances are expected to enter the environment from disposal because solid waste from the manufacturing, packaging, labeling, quality control testing, and distribution (i.e., waste resulting from rejected, returned or outdated substance/product) is disposed of by landfilling.

7. Fate of the Emitted Substances in the Environment:

7.1 Studies were done to determine the fate, transport, and transformation of the active drug, mirtazapine, in air, water and terrestrial ecosystems. Summaries for each environmental study conducted and test reports, including the experimental design, method and results, are provided in CONFIDENTIAL APPENDIX VIII.

7.1.1 Water Solubility

Measurement of the water solubility of mirtazapine was done at pH 4.9, 5.1, 7.0 and 9.0. The test article had a solubility of 462.7 g/L at pH 5.1 and 692.7 g/L at pH 4.9. The water solubility in pH 7.0 and pH 9.0 was 332.6 mg/L and 92.5 mg/L, respectively.

7.1.2 Octanol/Water Partition Coefficient

Mirtazapine was found to have a mean n-octanol/water partition coefficient of 1243.4 at pH 9 with a log K_{ow} 3.09. At pH 9 nearly all of the test article is in the unprotonated form. Values determined for pH 5 and pH 7 were in agreement with the value at pH 9 after correcting for the associated fraction. Based on the low log K_{ow} , mirtazapine in its neutral form is expected to have a moderate potential to bioconcentrate. At pH 7 and lower, the measured log K_{ow} values suggest a lower potential to bioconcentrate.

7.1.3 Vapor Pressure

The vapor pressure of [^3H]-mirtazapine was determined. The vapor pressure of the test article, 3.5×10^{-10} mm Hg at 25°C, is among the lowest known for organic chemicals. The test article is therefore not volatile and is not likely to be transported to other environmental compartments by air. The test article has an estimated Henry's Law Constant of 1.5×10^{-11} , which indicates that its vaporization from water would be negligible.

7.1.4 Dissociation Constant

A dissociation constant (pK_a) of 7.0 at 25°C in water was determined for mirtazapine. With respect to environmentally relevant pH of 5 to 9, mirtazapine is charged positively at low pH values and has potential to bind to soils. At high pH values, mirtazapine is neutral and capable of entering and passing through lipid membranes.

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7.1.5 Melting Temperature

The melting range of mirtazapine was determined by heating a pulverized sample of mirtazapine in a hot stage unit which is mounted under a microscope. Polarized light was used to observe the melting behavior. The melting range of mirtazapine was found to be 114.0°C to 115.2°C. No decomposition was observed and the white solid melted into a clear, light yellow liquid. No change of the state of the test article is expected at normal temperatures in the environment and its potential distribution within and between water, soil, and air will be minimal.

7.1.6 Density and Relative Density

The density of mirtazapine powder is 1.23 g/cm³ at 20°C. The relative density of mirtazapine powder is 1.23. This factor would not be expected to have any influence on the environment.

7.1.7 pH

The pH of a 1% (w/w) dispersion of mirtazapine in deionized CO₂-free water was determined to be 7.89 at 25.2°C.

7.1.8 Conclusion

Based on the above studies, it can be concluded that mirtazapine will enter the aquatic and terrestrial compartment.

7.2 The following studies were performed to determine the fate of mirtazapine in the aquatic and terrestrial compartment.

7.2.1 Ultraviolet-Visible Absorption Spectrum

The ultraviolet-visible absorption spectrum of mirtazapine was determined in methanol:water mixtures 1:1 (v/v) and in the same solvent mixtures at pH < 5 and pH > 9 in the spectral region between 290 nm and 800 nm at 25°C. Mirtazapine solutions in methanol:water mixtures 1:1 (v/v) show a maximum absorbance at 292 nm. The molar extinction coefficient at this wavelength is 6200 L.mol⁻¹cm⁻¹. Mirtazapine solutions at pH < 5 have no distinct maximum in the spectral range 290 nm to 800 nm. The maximum was found at 288 nm. Mirtazapine solutions at pH > 9 have a maximum absorbance at 295 nm. The molar extinction coefficient at this wavelength is 6100 L.mol⁻¹cm⁻¹.

7.2.2 Hydrolysis in Buffered Aqueous Solutions

Measurement of the hydrolysis of mirtazapine was determined for one concentration at pH 5.0, 7.0 and 9.0. The average analysis at each pH showed that less than 10% hydrolysis had occurred after five days at 50°C. Mirtazapine is considered hydrolytically stable with a half-life projected to be equal to or greater than a year. The test article is likely to slowly undergo change through hydrolytic mechanism when present in the aquatic media. This factor would not be expected to exert any negative influence on the environment.

7.2.3 Sorption and Desorption in Soils

Three soils, sandy loam, loam, and sand soils were evaluated. The results suggest significant sorption of the test article on all soil types tested and the mobility of the test article in these three soil types is likely to be low.

7.2.4 Aquatic Photodegradation

Measurement of the photodegradation of mirtazapine in aqueous solution was determined for one concentration at pH 5.0, 7.0 and 9.0. Photodegradation rate constants of 2.220, 1.980, and 0.468 h⁻¹ at pH 5, 7 and 9, respectively were determined. Half-lives of 0.31, 0.35, and 1.48 hours at pH 5, 7 and 9, respectively were calculated from these rate constants. Photodegradation may be considered to be an important mechanism of degradation.

7.2.5 Aerobic Biodegradation in Water

Mirtazapine does not degrade in water under aerobic conditions. The biodegradation in water is therefore not considered a major mechanism for the degradation of the test article.

7.2.6 Aerobic Biodegradation in Soils

The aerobic biodegradation of mirtazapine was evaluated in sandy loam, loam, and sand. Based on the results, biodegradation in these soils is not considered a major mechanism for the degradation of the test article.

7.2.7 Aerobic Biodegradation in Sediment and Sludge

No aerobic biodegradation of mirtazapine in ditch sediment and activated sludge was observed. Based on the results, biodegradation in sediment and activated sludge is not considered a major mechanism for the degradation of the test article.

7.2.8 Conclusion

Atmospheric volatilization is not relevant to the environmental fate of mirtazapine as the vapor pressure, at 3.5×10^{-10} mm Hg at 25°C, is among the lowest known for organic chemicals. Additionally, mirtazapine final disposition is burial in a landfill or is released to sewage treatment facilities where volatilization to the atmosphere is not an operating process. Mirtazapine is therefore not volatile and is not likely to be transported to other environmental compartments by air. Mirtazapine has an estimated Henry's law constant of 1.5×10^{-11} , which indicates that also its vaporization from water would be negligible.

Based on the above studies, mirtazapine will be removed from the sewage by binding to sludge in wastewater treatment facilities and by aquatic photodegradation. Aerobic biodegradation is not considered a major mechanism for degradation. Since sludge/sediment is disposed of by landfill (final disposal), the aquatic compartment is the principal compartment in which mirtazapine may have environment effects. If binding of mirtazapine onto sludge/sediment and photodegradation are not taken into consideration, the maximum expected emitted concentration will be less than 45.6 ng/L since the effluent of the wastewater treatment facilities will be further diluted by the surface water.

7.3 Metabolites

The chemical structure of the excreted metabolites are similar to that of the parent active drug, mirtazapine (see Section 5.3). In general, the physico-chemical characteristics of the excreted metabolites (conjugated metabolites) are more polar (hydrophilic) than mirtazapine. Thus, once excreted to the environment they are expected to have a lower volume of distribution because of their polarity, and as a result contamination to the environment would be restricted to the aquatic system (worse case exposure assumption being 45.6 ppt equivalent of metabolites rather than mirtazapine in the aquatic system). All metabolites have lower or no pharmacological activity compared to the parent drug, mirtazapine, and have been indirectly studied in pre-clinical toxicology studies with mirtazapine. Based on their structures, it is expected that these metabolites will behave in a similar manner as mirtazapine. Therefore, the environmental effects studies conducted with mirtazapine are also representative of effects related to the metabolites.

8. Environmental Effects of Released Substances

The following environmental effect studies have been performed with mirtazapine to determine its ecotoxicological effects in the water ecosystem. Summaries for each environmental study conducted and test reports including the experimental design, method and study results are provided on CONFIDENTIAL APPENDIX VIII.

8.1 Tests and Conclusions

8.1.1 Algal Assay

For the green alga, the "no observed effect limit" (NOEL) and the minimum inhibitory concentration (MIC) were 4.87 mg/L and 9.74 mg/L for the maximum standing crop and 19.5 mg/L and 39.0 mg/L for the maximum growth rate, respectively, within 14 days. For the blue-green alga, the NOEL and MIC were 9.74 mg/L and 19.5 mg/L for the maximum standing crop and 19.5 mg/L and 39.0 mg/L for the maximum growth rate, respectively, within 14 days. Since the maximum expected environmental concentration for mirtazapine is expected to be much lower, the test article does not pose any environmental concern.

8.1.2 Microbial Growth Inhibition

For the *Penicillium verrucosum*, the soil bacteria *Pseudomonas putida*, the ascomycete *Trichoderma hamatum*, and the nitrogen-fixing bacteria *Azotobacter sp.*, the Minimum Inhibitory Concentration (MIC) was higher than 292 mg/L. For the nitrogen-fixing blue-green alga, *Nostoc calcicola*, the MIC was 73.1 mg/L. Since the environment concentration of mirtazapine is expected to be much lower, it is expected that there will be no interference with natural degradative functions of the microorganisms.

8.1.3 *Daphnia* Acute Toxicity

The acute toxicity of mirtazapine to *Daphnia magna* (Straus), water flea, was investigated twice in a semi-static test system for a period of 48 hours. In concentrations > 3.95 mg/L subjective effects on mobility were observed, which could not be quantified. The EC₅₀ at 45 hours for mobility was 25.8 mg/L in Test 1 and 19.5 mg/L in Test 2.

8.1.4 *Daphnia* Chronic Toxicity

The chronic toxicity of mirtazapine to *Daphnia magna* (Straus), water flea was investigated in a semi-static system for a period of 21 days. The lowest observed effect concentration (LOEC) and the no observed effect concentration (NOEC) of the various end points were as follows:

	<u>NOEC</u>	<u>LOEC</u>
Mortality of Parent Animals:	1.95 mg/L	3.90 mg/L
Time of Production of First Brood:	0.97 mg/L	1.95 mg/L
Growth of the Parent Animals:	0.24 mg/L	0.49/mg/L
Reproduction (Total Offspring):	0.49 mg/L	0.97 mg/L
Reproduction (Mobile Offspring):	0.49 mg/L	0.97 mg/L

8.1.5 Fresh Water Fish Acute Toxicity

The acute toxicity of mirtazapine to the freshwater fish *Pimephales promelas* was investigated in a static test period of 96 hours. At concentrations of 2.53 mg/L and higher, effects on coloration, equilibrium and swimming behavior were found. The LOEC and NOEC for death was 5.06 mg/L, and 2.53 mg/L, respectively.

Since the maximum expected emitted concentration, 45.6 ppt is much lower than the lowest effective dose tested in the relevant acute toxicity test for the aquatic compartment, the overall conclusion is that emission of mirtazapine from the use of Remeron™ will not result in environmentally adverse effects.

8.1.6 Earthworm

Microbial inhibition testing, which is indicative for terrestrial environments, was conducted. The minimum inhibitory concentration for test fungi, soil bacteria, ascomycete, and nitrogen-fixing bacteria was greater than 292 mg/L, which far exceeds the MEEC. An earthworm study was not specifically conducted and not considered necessary.

Due to its strong sorptive capacity and lack of biodegradability, it is expected that virtually all the excreted drug substance will make its way to a wastewater treatment facility (Publicly Owned Treatment Waste Facility, or POTW). In a POTW, mirtazapine will be partly present in the aquatic phase and partly in the sludge phase. The size of the respective fractions is determined by the K_d values, as seen by the results of the adsorption/desorption experiments in the table below.

<u>Soil pH</u>	<u>K_d (with CaCl_2)</u>	<u>K_d (no CaCl_2)</u>
4.5	23.8	579.7
5.7	58.7	167.9
7.6	391.5	592.5

The values with CaCl_2 are most representative (since the influent to a POTW contains salts), and the average pH values of POTWs are between 6 and 7.5. Therefore, the K_d values of 58.7 to 391.5 are most applicable to the mirtazapine. Based on this, approximately 0.25% to 1.7% of the mirtazapine will exist in the aqueous phase, and an estimated 98% will exist in the adsorbed phase. This adsorbed fraction will have an average residence time of 10 days at POTW, and the amount of mirtazapine available for release to the environment will be a function of the amount of mirtazapine which remains sorbed to the sludge after aquatic photodegradation and anaerobic degradation have occurred.

Any mirtazapine which sorbed to the sludge, even after the extensive exposure in the POTW, will be taken with the sludge to appropriate landfills. The high sorption properties will ensure that mirtazapine which has not degraded will remain in the landfill, and therefore, no meaningful threat of exposure to the terrestrial organisms and environment will occur.

Based on the fact that exposure to soil is minimal and toxicity in soil microorganisms is at a much higher concentration, specific studies for the earthworm were considered not appropriate or meaningful.

8.1.7 Preclinical Toxicology

Available preclinical toxicology data on the acute and chronic toxicity of mirtazapine are provided in CONFIDENTIAL APPENDIX IX. Based on the information available, no adverse short or long-term effects are anticipated as a consequence of the release of mirtazapine into the environment at levels associated with the production, use and disposal of Remeron™ tablets.

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9. **Use of Resources and Energy:**

9.1 **Estimate of the Energy Requirement for the Manufacture of Mirtazapine for Marketing**

9.1.1 **The Netherlands**

Production of mirtazapine drug substance or Remeron™ tablets has been estimated to comprise approximately 3% of total energy use and water resources for drug production.

9.1.2 **The United States**

Packaging and distribution of Remeron™ tablets comprises less than 1% of total energy use and water resources at each of the sites at which Remeron™ is packaged and distributed. Quality control testing of Remeron™ tablets comprises less than 1% of total energy use and water resources at the West Orange facility.

9.2 **Effects upon Endangered or Threatened Species and upon Property Listed in National Register of Historic Places**

Since the drug substance and product will be manufactured at existing facilities outside the United States, there is no impact on endangered or threatened species, or upon property listing in the National Register of Historic Places in the United States, as a result of this action. Additionally, based on the findings of the environmental fate and effects testing and results, resource and energy use will not affect endangered or threatened species.

No impact on endangered or threatened species, or upon property listing in the National Register of Historic Places in the United States can be expected from the limited packaging, distribution and quality control testing conducted in the New Jersey and Pennsylvania area.

REDACTIONS MADE
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Facilities, buildings, equipment, and procedures for manufacturing packaging, distribution, and disposal of drug substance and drug product meet current standards of operation, i.e., building and energy regulations, both for the Netherlands, where production of drug substance and drug product is done, and for the United States, where packaging, labeling and testing of drug product is done. Controls exercised to mitigate potential adverse environmental impacts associated with operations have been described in Item 6. Standards under which production is operated include Good Manufacturing Practices, and internal procedures for safe handling of material. Internal and external inspections are done to help assure that these standards are maintained.

There is no potential adverse environmental impact from disposal of the drug product by consumers. In addition, the following practices are in place to mitigate potential adverse environmental impacts.

In the United States:

- (a) Spill control procedures and safe handling procedures are adhered to as required by Occupational Safety and Health Administration, the Environmental Protection Agency, the New Jersey Department of Environmental Protection and Organon Inc.'s company policy, as dictated by Standard Operating Procedures (SOPs).
- (b) No specific equipment systems are required since mirtazapine is not categorized as hazardous. Laboratory hoods are available to limit particle emissions to the laboratory during testing.
- (c) Control plans for spills or accidental release are detailed in Organon Inc.'s "Preparedness, Prevention and Contingency Plan, Chemical Hygiene Plan".
- (d) Training regarding hazardous materials, personal protective equipment, production equipment, SOPs and personal safety practices are conducted annually.

In The Netherlands:

- (a) Spill control procedures and safe handling procedures are adhered to as required by the applicable regulations in The Netherlands.
- (b) Equipment systems used to prevent emissions from exceeding established limits are provided in detail in Section 6.1.2 of this document.
- (c) Control plans for spills or accidental release are in place for each of the facilities in the Netherlands.
- (d) Procedures regarding hazardous materials, personal protective equipment and production equipment, SOPs and personal safety practices are followed. Laboratories have individual SOPs as well as company SOPs to cover safety practices.

11. Alternatives to the Proposed Action:

The only alternative to the proposed action is no action, which means that a new antidepressant with a minimal side effect profile, demonstrated to be safe and effective, will not be available to persons with depression who do not respond to other currently marketed antidepressants, or who will benefit by the anxiolytic and sleep-improving properties of this drug.

In addition, since findings of this report show that adverse environmental effects have not been identified with the proposed action to produce and market Remeron™ tablets; that manufacturing, packaging and testing of the product have not been associated with any known environmental impact because of the strict environmental controls and mitigation practices employed, there is unlikely to be significant risk of adverse environmental impact.

**REDACTIONS MADE
BY APPLICANT****12. Preparers:**

Lori A. Fiorentino
Documentation Assistant, Pharmaceutical Development Department
Organon Inc.
B.S., Biology
Monmouth University
West Long Branch, New Jersey
Two years industry experience in toxicology, one year in the development of new drug products.

Jay L. Rheingold, Ph.D.
Assistant Director, Pharmaceutical Development Department
Organon Inc.
Ph.D., Pharmaceutics
University of Connecticut
Storrs, Connecticut
Fifteen years industry experience in the development of new drug products, generics and OTC's.

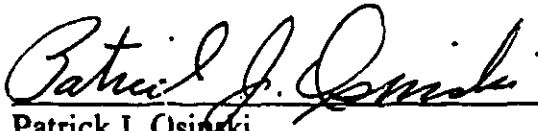
Philip W. Stern, Ph.D.
Director, Pharmaceutical Development Department
Organon Inc.
Ph.D., Pharmaceutical Chemistry
University of Michigan
Ann Arbor, Michigan
Twenty-five years industry experience in the development of new drug products.

Carol B. Shichman
Senior Regulatory Associate, Regulatory Affairs Department
Organon Inc.
B.S., Microbiology
University of Illinois
Champaign, Illinois
Ten years clinical research experience in regulatory affairs and in the development of new drug products.

Dr. Dolf Wijk
Ph.D. Aquatic Ecology
University of Nijmegen
Nine years experience in environmental policy and risk assessment, chemistry ecotoxicology and aquatic ecotoxicology

REDACTIONS MADE
BY APPLICANT13. **Certification**

The undersigned official certifies that the information presented is true, accurate, and complete to the best of the knowledge of the firm.



Patrick J. Osinski

Oct. 30, 1993
Date

Vice President, Product Development and Government Affairs

14. References:**14.1 References to Environmental Assessment Test Reports**

Albert, A. and Serjeant, E.P., "Ionization Constants of Acids and Bases", Methuen and Co. Ltd., London, John Wiley and Sons Inc., New York, 1962.

ASTM D 2117-82(88), "Standard Test Method for Melting Point of Semi-Crystalline Polymers by the Hot Stage Microscope Method".

ASTM C604-86 (1986), "Standard Test Method for True Specific Gravity of Refractory Materials by Gas Comparison Pycnometer".

Bartha, R. and Pramer, D. 1965, "Features of a Flask and Method for Measuring the Persistence and Biological Effects of Pesticides in Soil", Soil Sci. 100(1), pages 68 - 70.

Brohmer, 1977, "Fauna von Deutschland", 13th Edition, Quelle and Meyer.

de Ruiter, C., 1993, "Vapor Pressure of Mirtazapine", CRL F93173.

Draft O.E.C.D. Test Guideline, "Prolonged Toxicity Study with *Daphnia magna*, Effects on Reproduction", proposal for an update of the OECD Guideline 202, Part II, draft 06/05/1991.

EPA (U.S. Environmental Protection Agency), 1985, Toxic Substances Control Act Test Guidelines, Final Rule, Federal Register 50:39252-39263.

German Standard Methods for the Examination of Water, Wastewater and Sludge, Gaseous Components (Group G), Determination of Dissolved Oxygen, Electrochemical Probe Method (G22), DIN 38408, Part 22, November 1986.

Geurts, M.G.J. and Van Wijk, R.J., 1993, "Solubility of Mirtazapine in Water", CRLF93129.

Hamaker, J.W., 1975, "The Interpretation of Soil Leaching Experiments", pages 115 - 133, R. Hague and V.H. Freed (Eds.), Environmental Dynamics of Pesticides, Plenum Press, New York.

"Interim Guidance to The Pharmaceutical Industry for Environmental Compliance Requirements for the FDA", Pharmaceutical Manufacturers Association of the United States.

14.1 References to Environmental Assessment Test Reports (cont.)

ISO/TC 147/SC 5WG 4N152, German proposal for an ISO-standard, water quality evaluation in an aqueous medium of the ultimate aerobic biodegradability of organic compounds, method by analysis of biochemical oxygen demand (closed bottle test).

Kenaga, E.E., 1980, "Predicted Bioconcentration Factors and Soil Sorption Coefficient of Pesticides and Other Chemicals", *Ecotox. Environ. Saf.* 4, pages 1094 - 1099

L.G. van Uitert and C.G. Haas, *J. Amer. Chem. Soc.* 75 (1953), page 451.

M.A. Hamilton, P.C. Russo and R.V. Thurston, 1977, "Trimmed Spearman-Kärber Method for Estimating Median Lethal Concentrations in Toxicity Bioassays", *Env. Sci. & Technology* 11, pages 714 - 719. Correction 12 (1978) page 417.

Manual "Alkalinity", Merck, Darmstadt, Germany.

Manual "Beckman Instruments", 015-081142-F.

Manual Consort Laboratory Meters, Consort pvba, Turnhout, Belgium.

Manual "Photometric Precision Analysis", Dr. Lange, Dusseldorf, Germany, July 1989, page 120.

Manual "Water Hardness, Cuvette Test 327", Dr. Lange, Dusseldorf, Germany, Edition 90/06.

Mark, U.E., Arend, I.C.M., Geurts, M.J., de Ruiter C., 1993, "Acute Toxicity of Mirtazapine to *Daphnia magna*", CRL F93132.

Means et. al., *Environ. Sci. Technol.*, 16:93 - 98, 1982.

Memorandum of Understanding, 1988, Memorandum of Understanding between the Food and Drug Administration, Department of Health and Human Services, The United States of America and the Ministry of Welfare, Health and Cultural Affairs, The Netherlands, on Good Laboratory Practice. Approved by FDA, December 16, 1988 and by the Ministry of Welfare, Health and Cultural Affairs, December 20, 1988.

O.E.C.D., 1981. Principles of Good Laboratory Practice, C(81)30(FINAL)

O.E.C.D. Test Guidelines for Testing of Chemicals, Section 3, Degradation and Accumulation, Number 301 D, Ready biodegradability, closed bottle test (1982) Paris Cedex France.

14.1 References to Environmental Assessment Test Reports (cont.)

SAS, 1987. SAS Software package, SAS Institute Inc., Cary, North Carolina 27512-8000, USA, Release 6.03

Soil Survey Staff, 1975. Soil Taxonomy. "A Basic System of Soil Classification for Making and Interpreting Soil Surveys". Handbook Number 436. U.S. Department of Agriculture, Washington, D.C.

Standard test method for conducting aqueous direct photolysis test, E896, Section 11, Volume 11.04, Annual Book of ASTM Standards, 1988, Philadelphia, USA.

Stephan, C.E., 1977, "Methods for Calculating LC_{50} ", Aquatic Toxicology and Hazard Evaluation, F.L. Mayer and J.L. Hamelink (Eds.), pages 65 - 84

Streble, H., Krautner, D., 1988, "Das Leben im Wassertropfen", 8th Edition, Kosmos Naturführer.

U.S. Food and Drug Administration, 1987, FDA, Washington D.C.,
Environmental Assessment Handbook, Technical Assistance Documents:

- 3.01 Water Solubility
- 3.02 n-Octanol/Water Partition Coefficient
- 3.03 Vapor Pressure
- 3.04 Dissociation Constant
- 3.05 Ultraviolet-Visible Absorption Spectrum
- 3.06 Melting Temperature
- 3.07 Density and Relative Density
- 3.08 Sorption/Desorption
- 3.09 Hydrolysis
- 3.10 Aquatic Photodegradation
- 3.11 Aerobic Biodegradation
- 3.12 Aerobic Biodegradation in Soil
- 4.01 Growth Rate and Standing Crop of Two Algal Species (*Selenastrum apricornutum* and *Microcystis aeruginosa*)
- 4.02 Microbial Growth Inhibition
- 4.08 *Daphnia* Acute Toxicity
- 4.09 *Daphnia* Chronic Toxicity
- 4.11 Freshwater Fish Acute Toxicity
- 5.01 Acute Toxicity Calculations

REDACTIONS MADE
BY APPLICANT14.1 References to Environmental Assessment Test Reports (cont.)

van Ginkel, C.G., Stroo, C.A., 1992, "Simple Method to Prolong the Closed Bottle Test for the Determination of the Inherent Biodegradability", *Ecotoxicology and Environmental Safety* 24, pages 319 - 327.

van Houwelingen, G.D.B., Veenstra, G.J., 1993, "Dissociation Constant of Mirtazapine", CRL F93179.

van Houwelingen, G.D.B., Veenstra, G.J., 1993, "UV-Vis Spectrum of Mirtazapine", CRL F93122.

Williams, D.A. 1972, "The Comparison of Seven Dose Levels with a Zero-Dose Control", *Biometrics* 28, pages 519 - 531.

REDACTIONS MADE
BY APPLICANT**15. Appendices**

APPENDIX A:	Compliance Documentation from the Dutch Government
APPENDIX B:	Material Safety Data Sheets (MSDS) for the Excipients Used in the Manufacture of Remeron™ Tablets
CONFIDENTIAL APPENDIX I:	Information on the Impurities of Mirtazapine
CONFIDENTIAL APPENDIX II:	Process Flow Diagram for the Synthesis of Mirtazapine Drug Substance
CONFIDENTIAL APPENDIX III:	Process Flow Diagram for the Manufacture of Remeron™ Tablets
CONFIDENTIAL APPENDIX IV:	SDGRR-2290, "Biotransformation of ORG 3770 in Man and Laboratory Animals"
CONFIDENTIAL APPENDIX V:	Percent of Metabolites of Mirtazapine in Urine
CONFIDENTIAL APPENDIX VI:	RDGA-306, "Material Disposal" RDGA-533, "Handling and Disposal of Hazardous Waste Solvents"
CONFIDENTIAL APPENDIX VII:	Market Projections and MEEC Calculation for Remeron™ Tablets
CONFIDENTIAL APPENDIX VIII:	Environmental Assessment (ARLA Report) A. Index B. Summary of Test Results C. Test Reports
CONFIDENTIAL APPENDIX IX:	Preclinical Toxicology Data on Mirtazapine

0034A

REDACTIONS MADE
BY APPLICANT

APPENDIX A
COMPLIANCE DOCUMENTATION FROM THE DUTCH GOVERNMENT

Environmental Impact Assessment

Environmental Acts and Regulations applicable to the Diosynth production

Act/Regulation	Subject	Permit requirement
Hinderwet/Wet Geluidhinder/Wet Algemene Bepalingen Milieuhygiëne/Wet Milieubeheer (HW/WGh/WABM/WM)	Emissions to Air Soil and Ground-water Protection External Safety Noise Nuisance Environmental Management System (EMS)	from Province North-Brabant October 28, 1994 (annex I)
Lozings Verordening	Waste water discharge to local sewage system	no site specific permit required
Wet Verontreiniging Oppervlaktewateren (WVO)	Waste water discharge to Municipal Waste Water Treatment Plant	from Water Board "De Maaskant" October 19, 1994 (annex II)
Wet Chemische Afvalstoffen. (WCA)	Waste Treatment and Discharge (exclusive waste water)	no site specific permit required
Wet Milieugevaarlijke Stoffen (WMS)	Notification of New Substances Substances Information Labeling	notification of substances to ministry of VROM

REDACTIONS MADE
BY APPLICANT

Environmental Impact Assessment (continued)

WATERSCHAP DE MAASKANT



oss, 19 oktober 1994
ons kenmerk: MR/SR
bijlagen: - - -
onderwerp:

VERKLARING

De dijkstoel van het waterschap De Maaskant, ten deze handelend als overheidsorgaan belast met het waterkwaliteitsbeheer in het gebied van het waterschap voornoemd;

gezien het verzoek van Diosynth B.V. te Oss d.d. 27 september 1994, kenmerk V&M 941496.MM;

verklaart hierbij dat uit vanwege hem in 1993 uitgevoerde toezicht op de naleving van de bij zijn besluit van 19 december 1988 aan Akzo Pharma Nederland B.V. te Oss en zijn rechtverkrijgenden verleende vergunning, ingevolge de Wet verontreiniging oppervlaktewateren (Stb. 1981, 531) ten behoeve van de vestigingen Organon International B.V. en Diosynth B.V., beide gelegen aan Kloosterstraat 6 te Oss (Nederland), niet is gebleken van overtreding door vergunninghouder van enig bij of krachtens deze vergunning gesteld voorschrift.

De dijkstoel voornoemd verklaart hierbij tevens dat tot op heden door hem geen administratiefrechtelijke of strafrechtelijke sancties ten aanzien van vorenbedoelde vergunninghouder zijn getroffen, ter zake van het niet dan wel onvoldoende naleven van meergenoemde vergunning.

De dijkstoel,	
de griffier,	de dijkgraaf,
	
M.W.J. van Oorachot Loco	H.A. van Schijndel Loco

raadhuisklaan 30 5341 GM Oss, postbus 309 5340 AH Oss, telefoon 04120-33331* postrekening nr. 1071997




AKZO NOBEL

0037

REDACTIONS MADE
BY APPLICANT

Environmental Impact Assessment (continued)

Translation of the statement on the previous page

(Letterhead of the Water Board De Maaskant)

Oss, 19 October 1994

DECLARATION

The Dike Council of the Water Board De Maaskant, being the government authority responsible for maintenance of the water quality in the area of its jurisdiction;

having regard to the request by Diosynth B.V., Oss, dated 27 September 1994, reference number V&M 941496.MM;

and following its 1993 supervision for compliance with the permit issued on 19 December 1988 under the Pollution of Surface Waters Act (Stb. 1981, 531) to Akzo Pharma Nederland B.V., Oss on behalf of Organon International B.V. and Diosynth B.V., both situated at Kloosterstraat 6 in Oss (The Netherlands), hereby declares that no violation of the terms and conditions of the said permit has taken place.

The aforementioned Dike Council hereby also declares that it has thus far not brought any legal or administrative actions against the permit holder for insufficient or non-compliance with the conditions of the said permit.

The Dike Council

The Clerk

The Chairman

(signature)
M.W.J. van Oorschot

(signature)
H.A. van Schijndel



AKZO NOBEL

0038

REDACTIONS MADE
BY APPLICANT

Environmental Impact Assessment (continued)

INGEKOMEN 1 NOV. 1994



Provincie
Noord-Brabant

Dienst Waterstaat, Milieu en Vervoer

Provinciehuis
Brabantlaan 1
Correspondentie-adres:
Postbus 90151
5200 MC 's-Herengobosch
Telefax: 073 - 12 35 65

Telefoon 073 - 81 28 12

Ons kenmerk: 291333
Uw kenmerk : V&M 941496.MM
Afdeling : LGM
Doorkiesnr. : 812491
Bijlagen : -
Datum : 28 oktober 1994
Onderwerp : Verklaring adequate milieu-
vergunningen.

Akzo Nobel Diosynth BV
t.a.v. de heer M. van der Most
Postbus 20
5340 BH OSS

VERZONDEN

31 OKT. 1994

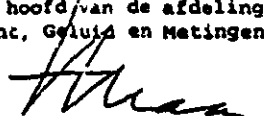
Geachte heer Van der Most,

Naar aanleiding van uw verzoek d.d. 27 september 1994,
kenmerk V&M 941496.MM verklaren wij hierbij:

- dat Akzo Pharma BV, moedermaatschappij van Diosynth BV, beschikt over vergunningen krachtens de Wet milieubeheer voor de door Diosynth BV uitgevoerde activiteiten. Deze vergunningen krachtens de Wet milieubeheer zijn door ons college afgegeven op respectievelijk 19 december 1989, 15 september 1992, 2 maart 1993 en 8 maart 1994;
- dat door ons college op de naleving van bovenvermelde vergunningen wordt toegezien;
- dat tot op heden door ons college geen bestuursrechtelijke of strafrechtelijke procedures zijn gestart om de naleving van de bovenvermelde vergunningen af te dwingen.

Wij vertrouwen erop u hiermede voldoende van dienst te zijn geweest.

Gedeputeerde Staten van Noord-Brabant,
namens desz.,
het hoofd van de afdeling
Lucht, Geluid en Metingen.


ir. R.D.M. Mass.

Bij antwoord s.v.p. onderwerp, datum en kenmerk van deze brief vermelden

Bezoekadres: ING Rekening nr. 67.45.80.043, Postbus nr. 1070178 t.n.v. Provincie Noord-Brabant


AKZO NOBEL

0639

REDUCTIONS MADE
BY APPLICANT

Environmental Impact Assessment (continued)

Translation of letter on previous page

(letterhead Province of North-Brabant)

Our ref.	: 291333	Akzo Nobel Diosynth BV
Op	: V&M 941496.MM	Your ref. attn. Mr. van der Most
Dept.	: LGM	P.O. Box no. 20
Direct line	: 812491	5340 BH OSS
Enclosures	: -	
Date	: 28 October 1994	
Subject	: Adequate Environmental Licences	

Dear Mr. van der Most,

With reference to your request dated 27 September, 1994, reference V&M 941496.MM, we hereby declare:

- that Akzo Pharma BV, mother company of Diosynth BV, is in possession of licences under the Environmental Act for the activities carried out by Diosynth. These licences under the Environmental Act were issued by our Board on 19 December, 1989, 15 September, 1992, 2 March, 1993 and 8 March, 1994 respectively;
- that our Board supervises the compliance with the above-mentioned licences;
- that our Board has thus far not commenced any legal or administrative actions to force compliance with the above-mentioned licences.

We trust we have been of sufficient help to you.

State Deputies of North-Brabant
On behalf of the above,
Head of the Air, Noise and
Measurements Department

Ir. H.D.M. Maas



AKZO NOBEL

0640

Ministry of Health, Welfare and Sport
Staatstoezicht op de volksgezondheid
Hoofdinspectie voor de geneesmiddelen
Rijswijk - Postbox 5406, The Netherlands

REDACTIONS MADE
BY APPLICANT

STATEMENT OF A MANUFACTURER

The undersigned, A.J. Smallenbroek, The Pharmaceutical Inspector in
The Netherlands herewith declares that:

- According to Netherlands Law

N.V. Organon
Kloosterstraat 6
5349 AB Oss, Holland

is licenced to manufacture and supply medicines by licence
number 2233 A/d.

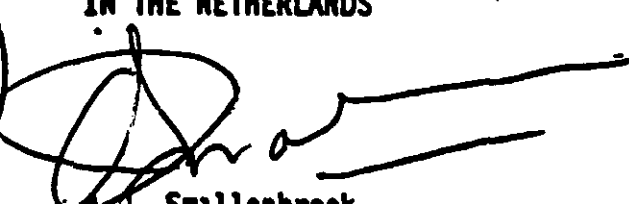
- This manufacturer conforms to principles and guidelines of
good manufacturing practice for medicinal products for human
use as is required by the directive 91/356/EEC which is
implemented in the national law. These requirements apply to
products to be sold or distributed within the country of
origin or to be exported.

The present statement is drawn up at the request of the interested
party in order to be submitted to the Health Authorities of
The United States of America

Rijswijk, November 29, 1994



THE PHARMACEUTICAL INSPECTOR
IN THE NETHERLANDS


A.J. Smallenbroek
Pharmacist

0041



No. 19.949

2223194

Ministry of Health, Welfare and Sport
Staatstoezicht op de Volksgezondheid
Hoofdinspectie voor de geneesmiddelen
Rijswijk - Postbox 5406, The Netherlands

REDACTIONS MADE
BY APPLICANT

CERTIFICATE OF PHARMACEUTICAL PRODUCT

Name and dosage form of product: REMERON 15 mg
tablets

Name and amount of each active ingredient:

Mirtazapine 15.0 mg

Manufacturer, and/or where applicable, the person responsible for placing the product on the market:

N.V. ORGANON
P.O. Box 20
Oss, Holland

It is certified that:

This product has been authorized to be placed on the market for use and is actually sold in this country.

Number of permit and date of issue: RVG 16685, March 15, 1994

It is also certified that (a) the manufacturing plant in which the product is produced is subject to inspections at suitable intervals, and (b) the manufacturer conforms to requirements for good practices in the manufacture and quality control, as recommended by the World Health Organization, in respect of products to be sold or distributed within the country of origin or to be exported.

The present statement is drawn up at the request of the interested party in order to be submitted to the Health Authorities of
The United States of America

Rijswijk, November 29, 1994

THE PHARMACEUTICAL INSPECTOR
IN THE NETHERLANDS

A.J. Smallegenbroek
Pharmacist

WHO 2/880125

0042



Ministry of Health, Welfare and Sport
Staatstoezicht op de Volksgezondheid
Hoofdinspectie voor de geneesmiddelen
Rijswijk - Postbox 5406, The Netherlands

CERTIFICATE OF PHARMACEUTICAL PRODUCT

REDACTIONS MADE
BY APPLICANT

Name and dosage form of product: REMERNON 30 mg
tablets

Name and amount of each active ingredient:

Mirtazapine 30,0 mg

Manufacturer, and/or where applicable, the person responsible for placing the product on the market:

N.V. ORGANON
P.O. Box 20
Oss, Holland

It is certified that:

This product has been authorized to be placed on the market for use and is actually sold in this country.

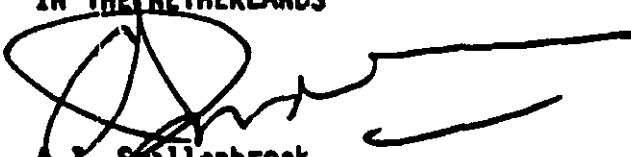
Number of permit and date of issue: RVG 16686, March 16, 1994

It is also certified that (a) the manufacturing plant in which the product is produced is subject to inspections at suitable intervals, and (b) the manufacturer conforms to requirements for good practices in the manufacture and quality control, as recommended by the World Health Organization, in respect of products to be sold or distributed within the country of origin or to be exported.

The present statement is drawn up at the request of the interested party in order to be submitted to the Health Authorities of
The United States of America

Rijswijk, November 29, 1994

THE PHARMACEUTICAL INSPECTOR
IN THE NETHERLANDS


A.J. Smalbroek
Pharmacist

WHO 2/880125

0043

**REDACTIONS MADE
BY APPLICANT**

**APPENDIX B
MATERIAL SAFETY DATA SHEETS (MSDS) FOR THE CHEMICAL
SUBSTANCES USED IN THE MANUFACTURE OF REMERON™ TABLETS**

REDACTIONS MADE
BY APPLICANT

MATERIAL SAFETY DATA SHEET

no. 92.379

Page 1

DIOSYNTH B.V.	P.O. BOX 20	5340 BH OSS	THE NETHERLANDS	Tel. 04120-61333
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SECTION I	
CHEMICAL NAME AND SYNONYMS:	1,2,3,4,10-14b-Hexamethylene-2-methyl-pyrrolidine-12,14b-epoxide (2,3,4,10,14b) hexazepine, ORG 3770.
CAS NO.:	88850-82-8 FORMULA: C ₁₇ H ₁₉ N ₃
COMMON NAME:	MINTAZAPINE

SECTION II - HAZARDOUS INGREDIENTS	
MATERIAL/COMPOSITION:	Not applicable.
NATURE OF HAZARD:	Not applicable.

SECTION III - PHYSICAL DATA	
MELTING POINT:	122 - 123 °C.
SOLUBILITY IN WATER:	Practically insoluble.
BOILING POINT:	Not applicable.
VAPOUR PRESSURE (mm Hg):	Not applicable.
VOLATILE BY VOLUME %:	Not applicable.
VAPOUR DENSITY (AIR = 1):	Not applicable.
EVAPORATION RATE:	Not applicable.
APPEARANCE AND COLOUR:	White to creamy white, crystalline powder. Odourless.

SECTION IV - FIRE AND EXPLOSION HAZARD DATA	
FLAMMABLE LIMITS:	LOWER: Not applicable. UPPER: Not applicable.
FLASH POINT (method used):	Not applicable.
FIRE EXTINGUISHING MEDIA:	Water, extinguishing powder, carbon dioxide or foam.
SPECIAL FIRE FIGHTING PROCEDURES:	Evacuate personnel to safe area. Fire-fighters should use self-contained breathing equipment and protective clothing.
UNUSUAL FIRE AND EXPLOSION HAZARDS:	Ground mechanical equipment in contact with dry material to dissipate the potential build up of static electricity as precaution against dust explosion.

SECTION V - HEALTH HAZARD DATA	
THERAPEUTICAL CATEGORY:	Antidepressive.
THRESHOLD LIMIT VALUE:	None established.
HAZARDS:	Routes of exposure: Inhalation, skin absorption and ingestion. Effects of over-exposure to vapour: Mucous membranes irritated, or absorbed through skin. Acute effects: Irritation can cause nausea, dizziness, headache, brownness and in rare cases effects on parasympathetic nerve system: orthostatic disturbance, effect: hyperaemia; blood effects: L500 (acute) 500 mg/kg (ORG 3770). Additional: May cause mild irritation to the eye and respiratory tract may cause sensitization by inhalation or skin contact.
FIRST AID PROCEDURES:	Inhalation: 1 Remove from exposure, fresh air, rest, if breathing is difficult, call a physician (show this Material Safety Data Sheet). Skin: 1 Flush with copious amounts of water while removing contaminated clothing and shoes. Call a physician (show this Material Safety Data Sheet). Eyes: 1 Flush with copious amounts of water for at least 15 minutes, separating eyelids with fingers. Call a physician. Ingestion: 1 Wash out mouth with water, provided person is conscious. Call a physician (show this Material Safety Data Sheet).

0046

REDACTIONS MADE
BY APPLICANT

no. 92.379

page 2

SECTION VI - REACTIVITY DATA	
STABILITY:	The product is stable. CONDITIONS TO AVOID: Not applicable.
INCOMPATIBILITY (materials to avoid):	Not applicable.
HAZARDOUS DECOMPOSITION PRODUCTS:	Nature of decomposition products not known.
HAZARDOUS POLYMERIZATION:	Will not occur. CONDITIONS TO AVOID: Not applicable.

SECTION VII - SPILL OR LEAK PROCEDURES	
SPILLS:	Vacuum or sweep up spillage and transfer into an appropriate container for waste disposal. Avoid dust. Ventilate area and wash spill site. Wear approved respirator and protective gloves.
DISPOSAL:	Disposal on chemical waste dump site or by incineration according to Federal, State or local laws.

SECTION VIII - SPECIAL PROTECTION			
RESPIRATORY PROTECTION: Dustmask e.g. 3M no. 8710.			
VENTILATION:	LOCAL: recommended	SPECIAL: Not applicable.	OTHER: Not applicable.
	GENERAL: recommended (Mechanical)		
PROTECTIVE GLOVES:	Chemically compatible.	EYE PROTECTION: Goggles.	
OTHER PROTECTIVE EQUIPMENT:	Wear a clean well fitted and closed overall. Change daily.		

SECTION IX - STORAGE CONDITIONS, HANDLING PRECAUTIONS	
HANDLING AND STORING:	Eating, drinking or smoking near material is forbidden. Store at 15 to 25 °C in well closed containers protected from light and moisture. Avoid breathing of dust. Avoid skin contact. In case of skin contact showering is necessary with lots of water and soap. Depending on the rate of exposure a supplied air respirator fixed fit type has to be used. After finishing work showering is necessary.

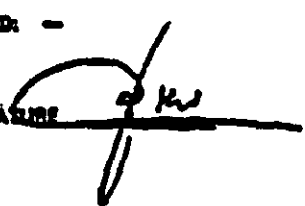
SECTION X - ADDITIONAL INFORMATION	

The information contained in this document is to our best knowledge true and accurate but all data, instructions, recommendations and/or suggestions are made without guarantee.

THIS SHEET SUPERSEDES MSDS NO. --

DATED: --

DATE ISSUED 3/3/93

SIGNATURE 

0047

END

MD