CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

76-122

Generic Name:	Mirtazapine Tablets, 15mg, 30mg, and 45mg
Sponsor:	Mylan Pharmaceuticals, Inc.
Approval Date:	June 19, 2003

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

76-122

CONTENTS

Reviews / Information Included in this ANDA Review.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

76-122

APPROVAL LETTER

ANDA 76-122

JUN 19 2003

Mylan Pharmaceuticals, Inc.
Attention: S. Wayne Talton
781 Chestnut Ridge Road
P.O. Box 4310
Morgantown, WV 26504-4310

Dear Sir:

This is in reference to your abbreviated new drug application (ANDA) dated February 27, 2001, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Mirtazapine Tablets, 15 mg, 30 mg, and 45 mg.

Reference is also made to our Tentative Approval letter dated January 15, 2002, and to your amendments dated June 13, 2001; January 2, May 12, May 16, and May 27, 2003. We also refer to your correspondence dated June 18, 2003 addressing patent issues explained in greater detail below.

The listed drug product referenced in your application, Remeron Tablets of Organon Inc., appears to be subject to a period of patent protection. As noted in the agency's publication entitled Approved Drug Products with Therapeutic Equivalence Evaluations, the "Orange Book", U.S. patent 5,977,099 (the '099 patent) is scheduled to expire on June 16, 2017. Your application contains a paragraph IV certification to the '099 patent under Section 505(j)(2)(A)(vii)(IV) of the Act stating that your manufacture, use, sale, offer for sale, or importation of Mirtazapine Tablets will not infringe on this patent, or that the patent is otherwise invalid and unenforceable. Section 505(j)(5)(B)(iii) of the Act provides that approval of an ANDA shall be made effective immediately, unless an action is brought against Mylan Pharmaceuticals, Inc. (Mylan) for infringement of the '099 patent which was the subject of the paragraph IV certification. This action must be brought against Mylan prior to the expiration of forty-five (45) days from the date the notice you provided under paragraph (2)(B)(i) was received by the NDA/patent holder(s). You notified the agency that Mylan complied with the requirements of Section 505(j)(2)(B) of the

Act, and that Organon Inc. initiated a patent infringement action in the United States District Court for the District of New Jersey (Azko Nobel N.V. and Organon Inc. v. Mylan Pharmaceuticals, Inc., Civil Action No. 01-03835 and 01-2171). You subsequently informed the agency that on December 18, 2002, the court entered Mylan's motion for summary judgement regarding the above litigation into the docket. This action represented an adjudication of non-infringement of the '099 patent.

The agency also recognizes that the eligibility for 180-day generic drug exclusivity under Section 505(j)(5)(B)(iv) of the Act awarded to TEVA Pharmaceuticals, Inc. for Mirtazapine Tablets 15 mg and 30 mg has expired. This exclusivity was triggered by TEVA's December 18, 2002, district court decision, and is also applicable to the 45 mg strength. Furthermore, with the expiration of eligibility for 180-day exclusivity for Mirtazapine Tablets 15 mg, 30 mg, and 45 mg, the agency has honored Organon Inc.'s request to remove the '099 patent from the Orange book.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Mirtazapine Tablets, 15 mg, 30 mg, and 45 mg, to be bioequivalent and, therefore, therapeutically equivalent to the listed drug, Remeron® Tablets, 15 mg, 30 mg, and 45 mg, respectively, of Organon, Inc. Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

Under Section 506A of the Act, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy that you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print.

Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-40). Please do not use Form FDA 2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-40) with a completed Form FDA 2253 at the time of their initial use.

Sincerely yours,

Gary Buehler 6/19/03
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

76-122

TENTATIVE APPROVAL LETTER(S)

ANDA 76-122

JAN 15 2002

Mylan Pharmaceuticals Inc.
Attention: Frank Sisto
781 Chestnut Ridge Road
P.O. Box 4310
Morgantown, WV 26504-4310

Dear Sir:

This is in reference to your abbreviated new drug application (ANDA) dated February 27, 2001, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (Act), for Mirtazapine Tablets, 15 mg, 30 mg, and 45 mg.

Reference is also made to your amendments dated June 13, June 29, October 25, 2001; and January 9, and January 15, 2002.

We have completed the review of this abbreviated application and have concluded that based upon the information you have presented to date, the drug is safe and effective for use as recommended in the submitted labeling. Therefore, the application is **tentatively approved**. This determination is based upon information available to the Agency at this time (i.e., information in your application and the status of current good manufacturing practices (cGMPs) of the facilities used in the manufacture and testing of the drug product). The determination is subject to change on the basis of new information that may come to our attention. This letter does not address notice issues related to the 180-day exclusivity provisions under section 505(j)(5)(B)(iv) of the Act.

The listed drug product referenced in your application, Remeron Tablets of Organon Inc. (sub. Akzona Inc.), is subject to a period of patent protection which expires on June 16, 2017, [U.S. Patent No. 5,977,099, (the '099

patent)]. Your application contains a Paragraph IV Certification to the '099 patent under Section 505(j)(2)(A)(vii)(IV) of the Act. The certification states that the '099 patent is invalid, unenforceable or will not be infringed by your manufacture, use, sale, offer for sale, or importation of this drug product. Section 505(j)(5)(B)(iii) of the Act provides that approval of an ANDA shall be made effective immediately, unless an action is brought against Mylan Pharmaceuticals Inc. (Mylan) for infringement of the patent that is the subject of the certification (the '099 patent). You have notified the agency that Mylan has complied with the requirements of Section 505(j)(2)(B) of the Act and that litigation is underway in the United States District Court for the District of New Jersey involving a challenge to the '099 patent (Akzo Nobel N.V. and Organon Inc. v. Mylan Pharmaceuticals Inc., Civil Action No. 01-3835 [FSH]). Therefore, final approval cannot be granted until:

1. a. the expiration of the 30-month period provided for in section 505(j)(5)(B)(iii) since the date of receipt of the 45-day notice required under section 505(j)(2)(B)(i), unless the court has extended or reduced the period because of the failure of either party to reasonably cooperate in expediting the action, or,

   b. the date of a court decision [505(j)(5)(B)(iii) (I), (II), or (III)], or,

   c. the patent has expired, and

2. The Agency is assured there is no new information that would affect whether final approval should be granted.

In order to reactivate your application prior to final approval, please submit a MINOR AMENDMENT - FINAL APPROVAL REQUESTED approximately 90 days prior to the date you believe your application may be considered for final approval. Your amendment must provide:

1. A copy of a court order or judgement, a settlement agreement between the parties, a licensing agreement between you and the patent holder, or any other relevant information, and

2. a. updated information related to final-printed labeling or chemistry, manufacturing and controls data, or any other change in the conditions outlined in this abbreviated application, or

   b. a statement that no such changes have been made to the application since the date of tentative approval.

Any changes in the conditions outlined in this abbreviated application and the status of the manufacturing and testing facilities' compliance with current good manufacturing procedures are subject to Agency review before final approval of the application will be made.

In addition to, or instead of, the amendments referred to above, the Agency may, at any time prior to the final date of approval, request that you submit amendments containing the information requested above.

Failure to submit either or both amendments may result in rescission of this tentative approval determination, or delay in issuance of the final approval letter.

The drug product that is the subject of this abbreviated application may not be marketed without final Agency approval under section 505 of the Act. The introduction or delivery for introduction into interstate commerce of this drug before the effective final approval date is prohibited under section 501 of the Act. Also, until the Agency issues the final approval letter, this drug product will not be listed in the Agency's "Approved Drug Products with Therapeutic Equivalence Evaluations" list.

The amendment requesting final approval should be designated as a MINOR AMENDMENT - FINAL APPROVAL REQUESTED

in your cover letter. Should you have additional questions about the status of this application, please contact Mark Anderson, R.Ph., Project Manager, at 301-827-5789.

Sincerely yours,

Gary Buehler
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

1/15/02

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

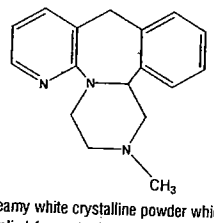
76-122

FINAL PRINTED LABELING

MIRTAZAPINE TABLETS
15 mg, 30 mg and 45 mg

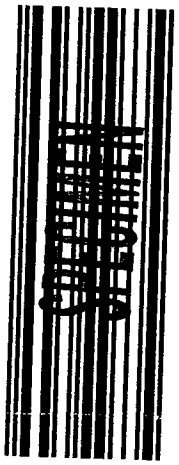
℞ only

DESCRIPTION: Mirtazapine Tablets are an orally administered drug. Mirtazapine has a tetracyclic chemical structure and 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 molecular 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.

Mirtazapine tablets are supplied for oral administration as scored film-coated tablets containing 15 mg or 30 mg of mirtazapine, and unscored film-coated tablets containing 45 mg of mirtazapine. Each tablet also contains the following inactive ingredients: anhydrous lactose, colloidal silicon dioxide, croscarmellose sodium, FD&C blue no. 2 lake, FD&C yellow no. 6 lake, hypromellose, magnesium stearate, microcrystalline cellulose, polydextrose, polyethylene glycol, pregelatinized (corn) starch, sodium lauryl sulfate, titanium dioxide and triacetin.



CLINICAL PHARMACOLOGY: Pharmacodynamics: The mechanism of action of mirtazapine, as with other drugs effective in the treatment of major depressive disorder, 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-HT_2 and 5-HT_3 receptors. Mirtazapine has no significant affinity for the 5-HT_{1A} and 5-HT_{1B} receptors.

Mirtazapine is a potent antagonist of histamine (H_1) 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: Mirtazapine is rapidly and completely absorbed following oral administration and have a half-life of about 20 to 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 to 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 mcg/mL.

Special Populations: ***Geriatric:*** Following oral administration of mirtazapine 20 mg/day for 7 days to subjects of varying ages (range, 25 to 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 mirtazapine to elderly patients (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Pediatrics: Safety and effectiveness of mirtazapine in the pediatric population have not been established (see PRECAUTIONS).

Gender: The mean elimination half-life of mirtazapine after oral administration ranges from approximately 20 to 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) (see Pharmacokinetics).

Race: There have been no clinical studies to evaluate the effect of race on the pharmacokinetics of mirtazapine.

Renal Insufficiency: The disposition of mirtazapine was studied in patients with varying degrees of renal function. Elimination of mirtazapine is correlated with creatinine clearance. Total body clearance of mirtazapine was reduced approximately 30% in patients with moderate (Clcr = 11 to 39 mL/min/1.73 m^2) and approximately 50% in patients with severe (Clcr = < 10 mL/min/1.73 m^2) renal impairment when compared to normal subjects.

Caution is indicated in administering mirtazapine to patients with compromised renal function (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Hepatic Insufficiency: 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 mirtazapine to patients with compromised hepatic function (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Clinical Trials Showing Effectiveness: The efficacy of mirtazapine tablets as a treatment for major depressive disorder was established in four placebo-controlled, 6-week trials in adult outpatients meeting DSM-III criteria for major depressive disorder. 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 s[illegible] 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: Mirtazapine Tablets are indicated for the treatment of major depressive disorder. The efficacy of mirtazapine in the treatment of major depressive disorder 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 effectiveness of mirtazapine in hospitalized depressed patients has not been adequately studied. The physician who elects to use mirtazapine for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient.

CONTRAINDICATIONS: 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 mirtazapine tablets developed agranulocytosis (absolute neutrophil count (ANC) < 500/mm^3 with associated signs and symptoms, e.g., fever, infection, etc.) and a third patient developed severe neutropenia (ANC < 500/mm^3 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 mirtazapine 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 mirtazapine should be discontinued and the patient should be closely monitored.

MAO Inhibitors: In patients receiving other drugs for major depressive disorder in combination with a monoamine oxidase inhibitor (MAOI) and in patients who have recently discontinued a drug for major depressive disorder 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 mirtazapine tablets, 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.

PRECAUTIONS: General: ***Somnolence:*** In U.S. controlled studies, somnolence was reported in 54% of patients treated with mirtazapine tablets, compared to 18% for placebo and 60% for amitriptyline. In these studies, somnolence resulted in discontinuation for 10.4% of mirtazapine treated patients, compared to 2.2% for placebo. It is unclear whether or not tolerance develops to the somnolent effects of mirtazapine. Because of mirtazapine'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 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 mirtazapine.

Increased Appetite/Weight Gain: In U.S. controlled studies, appetite increase was reported in 17% of patients treated with mirtazapine, compared to 2% for placebo and 6% for amitriptyline. In these same trials, weight gain of ≥ 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 mirtazapine discontinued for weight gain. In an 8-week long pediatric clinical trial of doses between 15 and 45 mg/day, 49% of mirtazapine-treated patients had a weight gain of at least 7%, compared to 5.7% of placebo-treated patients (see PRECAUTIONS: Pediatric Use).

Cholesterol/Triglycerides: In U.S. controlled studies, nonfasting cholesterol increases to ≥ 20% above the upper limits of normal were observed in 15% of patients treated with 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% (8/424) of patients exposed to mirtazapine in a pool of short-term U.S. controlled trials, compared to 0.3% (1/328) of placebo patients and 2% (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 mirtazapine treatment. Mirtazapine should be used with caution in patients with impaired hepatic function (see CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION).

Activation of Mania/Hypomania: Mania/hypomania occurred in approximately 0.2% (3/1,299 patients) of 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.

Seizure: In premarketing clinical trials only one seizure was reported among the 2,796 U.S. and non-U.S. patients treated with 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 major depressive disorder and may persist until significant remission occurs. As with any patient receiving drugs effective in the treatment of major depressive disorder, high-risk patients should be closely supervised during initial drug therapy. Prescriptions of 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 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 associated with significant orthostatic hypotension in early clinical pharmacology

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Increased Appetite/Weight Gain: In U.S. controlled studies, appetite increase was reported in 17% of patients treated with mirtazapine, compared to 2% for placebo and 6% for amitriptyline. In these same trials, weight gain of ≥ 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 mirtazapine discontinued for weight gain. In an 8-week long pediatric clinical trial of doses between 15 and 45 mg/day, 49% of mirtazapine-treated patients had a weight gain of at least 7%, compared to 5.7% of placebo-treated patients (see PRECAUTIONS: Pediatric Use).

Cholesterol/Triglycerides: In U.S. controlled studies, nonfasting cholesterol increases to ≥ 20% above the upper limits of normal were observed in 15% of patients treated with 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% (8/424) of patients exposed to mirtazapine in a pool of short-term U.S. controlled trials, compared to 0.3% (1/328) of placebo patients and 2% (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 mirtazapine treatment. Mirtazapine should be used with caution in patients with impaired hepatic function (see CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION).

Activation of Mania/Hypomania: Mania/hypomania occurred in approximately 0.2% (3/1,299 patients) of 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.

Seizure: In premarketing clinical trials only one seizure was reported among the 2,796 U.S. and non-U.S. patients treated with 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 major depressive disorder and may persist until significant remission occurs. As with any patient receiving drugs effective in the treatment of major depressive disorder, high-risk patients should be closely supervised during initial drug therapy. Prescriptions of 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 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 associated with significant orthostatic hypotension in early clinical pharmacology trials with normal volunteers. Orthostatic hypotension was infrequently observed in clinical trials with depressed patients. Mirtazapine 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 to 39 mL/min/1.73 m^2] and severe [GFR < 10 mL/min/1.73 m^2] renal impairment, and also in patients with hepatic impairment. Caution is indicated in administering mirtazapine to such patients (see CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION).

Information for Patients: Physicians are advised to discuss the following issues with patients for whom they prescribe mirtazapine:

Agranulocytosis: Patients who are to receive 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: 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 mirtazapine therapy does not adversely affect their ability to engage in such activities.

Completing Course of Therapy: While patients may notice improvement with 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 mirtazapine to interact with other drugs.

Alcohol: The impairment of cognitive and motor skills produced by 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 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 mirtazapine tablets 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 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 mirtazapine (15 mg) in 6 healthy male subjects. However, the impairment of cognitive and motor skills produced by mirtazapine were shown to be additive with those produced by alcohol. Accordingly, patients should be advised to avoid alcohol while taking mirtazapine.

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 mirtazapine 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 mirtazapine.

Carcinogenesis, Mutagenesis, Impairment of Fertility: ***Carcinogenesis:*** Carcinogenicity studies were conducted with 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/m^2 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 mirtazapine.

Mutagenesis: Mirtazapine 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, mirtazapine was given at doses up to 100 mg/kg (20 times the maximum recommended human dose (MRHD) on a mg/m^2 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/m^2 basis, respectively), have revealed no evidence of teratogenic effects. However, in rats, there was an increase in 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 20 times the MRHD, but not at 3 times the MRHD, on a mg/m^2 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 mirtazapine tablets are administered to nursing women.

Pediatric Use: Safety and effectiveness in pediatric patients have not been established. In an 8-week long pediatric clinical trial of doses between 15 and 45 mg/day, 49% of mirtazapine-treated patients had a weight gain of at least 7%, compared to 5.7% of placebo treated patients. The mean increase in weight was 4 kg (2 kg SD) for mirtazapine-treated patients versus 1 kg (2 kg SD) for placebo-treated patients (see PRECAUTIONS: Increased Appetite/Weight Gain).

Geriatric Use: Approximately 190 elderly individuals (≥ 65 years of age) participated in clinical studies with mirtazapine. This drug is known to be substantially excreted by the kidney (75%), and the risk of decreased clearance of this drug is greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection. Sedating drugs may cause confusion and over-sedation in the elderly. 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 mirtazapine 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 mirtazapine tablets in U.S. 6-week controlled clinical trials discontinued treatment due to an adverse experience, compared to 7 percent of 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 U.S. Mirtazapine Trials

Adverse Event	Percentage of Patients Discontinuing with Adverse Event	
	Mirtazapine (n=453)	Placebo (n=361)
Somnolence	10.4%	2.2%
Nausea	1.5%	0%

Commonly Observed Adverse Events in U.S. Controlled Clinical Trials: The most commonly observed adverse events associated with the use of mirtazapine (incidence of 5% or greater) and not observed at an equivalent incidence among placebo-treated patients (mirtazapine incidence at least twice that for placebo) were:

Common Treatment-Emergent Adverse Events Associated with the Use of Mirtazapine in 6-Week U.S. Trials

Adverse Event	Percentage of Patients Reporting Adverse Event	
	Mirtazapine (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 Mirtazapine-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 mirtazapine-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 EXPERIENCES[1] (≥ 1%) IN SHORT-TERM U.S. CONTROLLED STUDIES

Body System Adverse Clinical Experience	Mirtazapine (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 mirtazapine are included, except the following events which had an incidence on placebo ≥ mirtazapine: 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: The electrocardiograms for 338 patients who received mirtazapine and 261 patients who received placebo in 6-week, placebo-controlled trials were analyzed. Prolongation in QTc ≥ 500 msec was not observed among mirtazapine-treated patients; mean change in QTc was +1.6 msec for mirtazapine and −3.1 msec for placebo. Mirtazapine was associated with a mean increase in heart rate of 3.4 bpm, compared to 0.8 bpm for placebo. The clinical significance of these changes is unknown.

Other Adverse Events Observed During the Premarketing Evaluation of Mirtazapine: During its premarketing assessment, multiple doses of mirtazapine tablets were administered to 2,796 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 2,796 patients exposed to multiple doses of mirtazapine who experienced an event of the type cited on at least one occasion while receiving mirtazapine. 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 mirtazapine, 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:* pathologic 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.

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

DRUG ABUSE AND DEPENDENCE: Controlled Substance Class: Mirtazapine Tablets are not a controlled substance.

Physical and Psychological Dependence: Mirtazapine has not been systematically studied in animals or humans for its potential for abuse, tolerance or physical dependence. While 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 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 mirtazapine was in combination with amitriptyline and chlorprothixene in a non-U.S. clinical study. Based on plasma levels, the mirtazapine dose taken was 30 to 45 mg, while plasma levels of amitriptyline and chlorprothixene 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 mirtazapine alone.

Overdose Management: Treatment should consist of those general measures employed in the management of overdose with any drug effective in the treatment of major depressive disorder.

Ensure an adequate airway, oxygenation, and ventilation. Monitor cardiac rhythm and vital signs. General supportive and symptomatic measures are also recommended. Induction of emesis is not recommended. Gastric lavage with a large-bore orogastric tube with appropriate airway protection, if needed, may be indicated if pe
patients.

Activated charcoal should be administered.
diuresis, dialysis, hemoperfusion or exchange t
dosage. No specific antidotes for mirtazapine ar

In managing overdosage, consider the possit
should consider contacting a poison control cen
any overdose. Telephone numbers for certified p
Desk Reference (PDR).

DOSAGE AND ADMINISTRATION: Initial Treatr
tazapine Tablets is 15 mg/day, administered in
sleep. In the controlled clinical trials establishin
major depressive disorder, the effective dose ran
tionship between dose and satisfactory respons
for mirtazapine has not been adequately explor
dose may benefit from dose increases up to a m

Mirtazapine has an elimination half-life of
changes should not be made at intervals of less t
time for evaluation of the therapeutic response t

Elderly and Patients with Renal or Hepatic Impa
in elderly patients and in patients with moderate
quently, the prescriber should be aware that plas
patient groups, compared to levels observed in
ment (see PRECAUTIONS and CLINICAL PHARM

Maintenance/Extended Treatment: It is general
quire several months or longer of sustained ph
acute episode. It is unknown whether or not th
treatment is identical to the dose needed to achi
odically reassessed to determine the need for m
for such treatment.

Switching Patients To or From a Monoamine O
between discontinuation of an MAOI and initiatio
at least 14 days should be allowed after stopping

HOW SUPPLIED: Mirtazapine Tablets are availab
tazapine.

The 15 mg tablets are beige film-coated, rou
bossed with **M** over **515** on one side of the tablet
are available as follows:

NDC 0378
bottles of
NDC 0378
bottles of 1

The 30 mg tablets are beige film-coated, rou
bossed with **M** over **530** on one side of the tablet
are available as follows:

NDC 0378
bottles of
NDC 0378
bottles of 1

The 45 mg tablets are beige film-coated, roun
debossed with **M** over **545** on one side of the tat
able as follows:

NDC 0378
bottles of
NDC 0378
bottles of 1
NDC 0378
bottles of 5

STORE AT CONTROLLED ROOM TEMPERATURE
PROTECT FROM LIGHT AND MOISTURE.

Dispense in a tight, light-resistant container as
sure.

MYL

Mylan Pharma
Morgantown,

+1.6 msec for mirtazapine and –3.1 msec for placebo. Mirtazapine was associated with a mean increase in heart rate of 3.4 bpm, compared to 0.8 bpm for placebo. The clinical significance of these changes is unknown.

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Physical and Psychological Dependence: Mirtazapine has not been systematically studied in animals or humans for its potential for abuse, tolerance or physical dependence. While 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 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 mirtazapine was in combination with amitriptyline and chlorprothixene in a non-U.S. clinical study. Based on plasma levels, the mirtazapine dose taken was 30 to 45 mg, while plasma levels of amitriptyline and chlorprothixene 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 mirtazapine alone.

Overdose Management: Treatment should consist of those general measures employed in the management of overdose with any drug effective in the treatment of major depressive disorder.

Ensure an adequate airway, oxygenation, and ventilation. Monitor cardiac rhythm and vital signs. General supportive and symptomatic measures are also recommended. Induction of emesis is not recommended. Gastric lavage with a large-bore orogastric tube with appropriate airway protection, if needed, may be indicated if performed soon after ingestion, or in symptomatic patients.

Activated charcoal should be administered. There is no experience with the use of forced diuresis, dialysis, hemoperfusion or exchange transfusion in the treatment of mirtazapine overdosage. No specific antidotes for mirtazapine are known.

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. Telephone numbers for certified poison control centers are listed in the *Physicians' Desk Reference* (PDR).

DOSAGE AND ADMINISTRATION: Initial Treatment: The recommended starting dose for Mirtazapine Tablets is 15 mg/day, administered in a single dose, preferably in the evening prior to sleep. In the controlled clinical trials establishing the efficacy of mirtazapine in the treatment of major depressive disorder, the effective dose range was generally 15 to 45 mg/day. While the relationship between dose and satisfactory response in the treatment of major depressive disorder for mirtazapine 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.

Mirtazapine has an elimination half-life of approximately 20 to 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 PRECAUTIONS and CLINICAL PHARMACOLOGY).

Maintenance/Extended Treatment: It is generally agreed that acute episodes of depression require several months or longer of sustained pharmacological therapy beyond response to the acute episode. It is unknown whether or not the dose of mirtazapine needed for maintenance treatment is identical to the dose needed to achieve an initial response. Patients should be periodically reassessed to determine the need for maintenance treatment and the appropriate dose for such treatment.

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 mirtazapine tablets. In addition, at least 14 days should be allowed after stopping mirtazapine before starting an MAOI.

HOW SUPPLIED: Mirtazapine Tablets are available containing 15 mg, 30 mg and 45 mg of mirtazapine.

The 15 mg tablets are beige film-coated, round, biconvex, beveled edge, scored tablets debossed with **M** over **515** on one side of the tablet and bisected by a score on the other side. They are available as follows:

NDC 0378-3515-93
bottles of 30 tablets
NDC 0378-3515-01
bottles of 100 tablets

The 30 mg tablets are beige film-coated, round, biconvex, beveled edge, scored tablets debossed with **M** over **530** on one side of the tablet and bisected by a score on the other side. They are available as follows:

NDC 0378-3530-93
bottles of 30 tablets
NDC 0378-3530-01
bottles of 100 tablets

The 45 mg tablets are beige film-coated, round, biconvex, beveled edge, unscored tablets debossed with **M** over **545** on one side of the tablet and blank on the other side. They are available as follows:

NDC 0378-3545-93
bottles of 30 tablets
NDC 0378-3545-01
bottles of 100 tablets
NDC 0378-3545-05
bottles of 500 tablets

STORE AT CONTROLLED ROOM TEMPERATURE 15° TO 30°C (59° TO 86°F) [See USP].
PROTECT FROM LIGHT AND MOISTURE.

Dispense in a tight, light-resistant container as defined by the USP using a child-resistant closure.

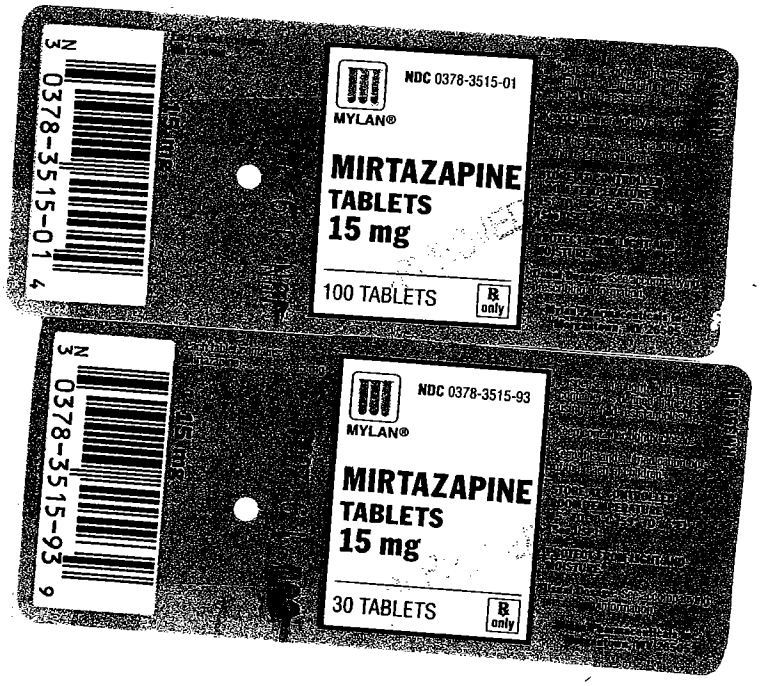
MYLAN®

Mylan Pharmaceuticals Inc.
Morgantown, WV 26505

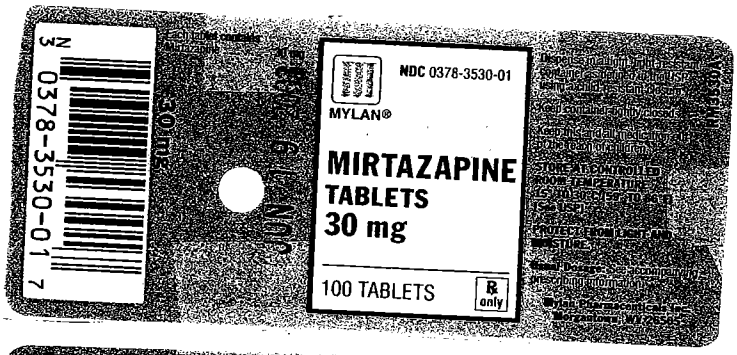
REVISED MAY 2003
MTZP:R4

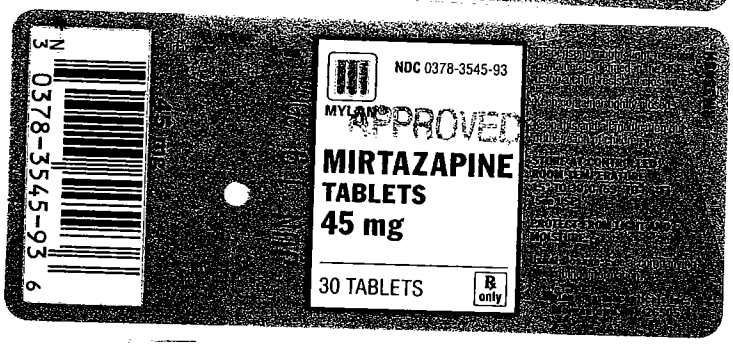
76-122

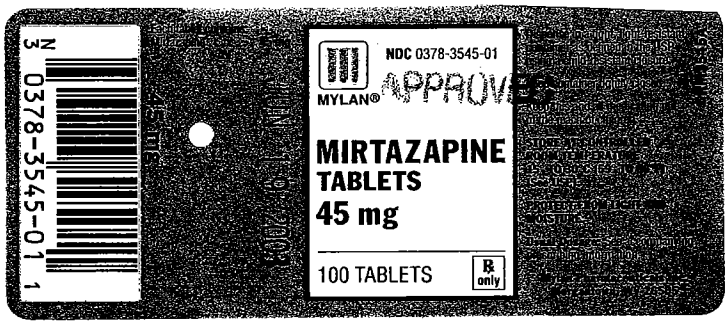
AP 6/1/03

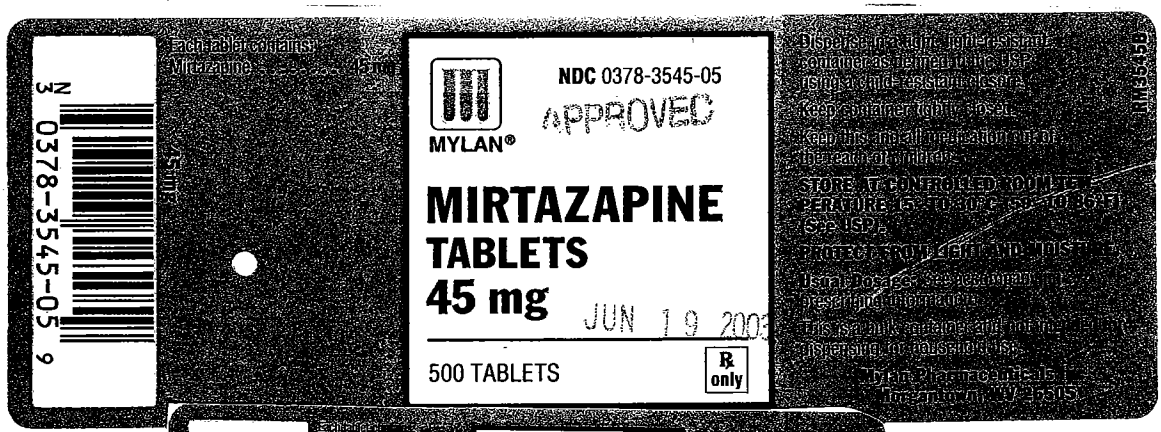


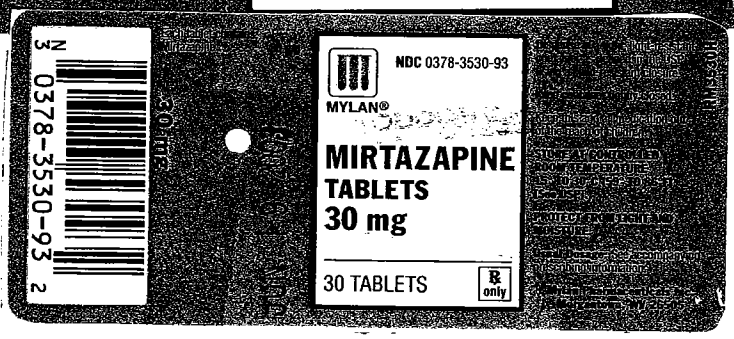
76-122
AP 6/1/03











CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

76-122

CSO LABELING REVIEW(S)

APPROVAL SUMMARY
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: **76-122**

Date of Submissions: **May 27, 2003**
May 16, 2003
May 12, 2003

Applicant's Name: **Mylan Pharmaceuticals Inc.**

Established Name: **Mirtazapine Tablets 15 mg, 30 mg and 45 mg**

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):
Do you have 12 Final Printed Labels and Labeling? Yes
Container Labels: 30s, 100s (all 3 strengths) and 500s (45 mg)
Satisfactory in FPL as of January 2, 2003 submission. (45 mg)
Satisfactory in FPL as of May 27, 2003 submission (15 mg and 30 mg)
Professional Package Insert Labeling:
Satisfactory in FPL as of May 16, 2003 submission.(Vol 6.1; Rev.May 2003;Code MTZP:R4)

Revisions needed post-approval:
GENERAL- Mylan commits to revise the storage temperature to 20°-25°C (68°-77°F) [see USP controlled room temperature].
INSERT – PRECAUTIONS, Transaminase Elevations, first sentence –change "—" to "≥".

BASIS OF APPROVAL:

Patent Data – 20-415

No	Expiration	Use Code	Use	File
5,977,099	6-16-17		Pharmaceutical composition comprising mirtazapine and one or more selective serotonin reuptake inhibitors	IV

Exclusivity Data - 20-415

Code/sup	Expiration	Use Code	Description		Labeling Impact
S-009	4-9-05	M-18	INFORMATION DENOTING THE EFFICACY OF REMERON IN MAINTAINING A RESPONSE IN PATIENTS WITH MAJOR DEPRESSIVE DISORDER (MDD)		Changes to CLINICAL PHARMACOLOGY, PRECAUTIONS and DOSAGE AND ADMINISTRATION

Was this approval based upon a petition? No
What is the RLD on the 356(h) form: Remeron® Tablets
NDA Number: 20-415
NDA Drug Name: Remeron® (mirtazapine) Tablets
NDA Firm: Organon

Date of Approval of NDA Insert and supplement #: 4/9/02 (S-009) and 9/30/02 (S-015)
Has this been verified by the MIS system for the NDA? Yes
Was this approval based upon an OGD labeling guidance? No
Basis of Approval for the Container Labels: side-by-sides
Other:

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured.		X	
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?		X	
Error Prevention Analysis			
Has the firm proposed a proprietary name? No.		X	
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.	X		
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			X
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?		X	
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		X	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		X	
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?		X	
Has the firm failed to describe the scoring in the HOW SUPPLIED section? THEY HAVE STATED THAT THE 15 mg and the 30 mg are scored but they have not stated that the 45 mg are unscored		X	
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		X	
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)		X	
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Because of proposed packaging configuration or for any other reason, does this applicant meet fail to meet all of the unprotected conditions of use of referenced by the RLD?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?			X
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		X	

Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		X	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?	X		
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.			

FOR THE RECORD: (portions taken from previous review)

1. Review based on the labeling of Remeron® (NDA 20-415/S-009), approved 4/9/02 and S-015, approved 9/30/02.
   The firm has sought pediatric exclusivity for their pediatric clinical studies, however they were denied exclusivity because of their failure to obtain longer-term safety data as required under the written request. (See file folder)

2. Patent/Exclusivities:

   one patent – 5977099 – 6/16/17
   M 18 exclusivity
   The firm has filed a Paragraph IV certification to the patent.

Summary of labeling changes as a result of the above exclusivity:

a. CLINICAL PHARMACOLOGY

   Last paragraph of section - describing a longer-term study - was carved out.

b. INDICATIONS AND USAGE (Third paragraph)

   i. First sentence revised.

   ii. Second sentence deleted.

   iii. Last sentence revised

c. PRECAUTIONS (Use in Patients with Concomitant Illness)

   Second sentence deleted.

d. ADVERSE REACTIONS

   i. ECG Changes subsection revised

   ii. New subsection added as last subsection.

e. DOSAGE AND ADMINISTRATION

   Maintenance/Extended Treatment subsection revised.

3. Labeling

   Mylan submitted an amendment for approval of the 45 mg strength only on 1/2/03. Mylan believes they are the first to file a paragraph IV for this strength and would be entitled to 180 day

exclusivity. Teva would be eligible for 180 day exclusivity for the 15 mg and 30 mg strengths. Mylan is now submitting an amendment for all 3 strengths (15 mg, 30 mg and 45 mg).

4. Mylan is the manufacturer (p 2995 v 1.1).

5. The drug product will be made available in container sizes of 30s (CRC),100s (CRC) and 500s (non-CRC)

6. The inactives are accurately listed in the DESCRIPTION section.

7. The tablet descriptions are accurate as seen in the HOW SUPPLIED section.

8. Storage Conditions:
NDA – Store at controlled room temperature 20°-25°C (68°-77°F).
ANDA – Store at controlled room temperature 15° to 30°C (59° to 86°F)(see USP). PROTECT FROM LIGHT AND MOISTURE.
USP – not USP

9. Dispensing Recommendations:
NDA – Dispense in a tight, light-resistant container as described in the USP.
ANDA – Dispense in a tight, light-resistant container as defined by the USP using a child-resistant closure.
USP – not USP

10. Scoring:
NDA –15 mg and 30 mg -scored, 45 mg - unscored
ANDA - same as NDA

Date of Review: **5-28-03**

Date of Submissions: **5-27-03**
5-16-03
5-12-03

Primary Reviewer: **Michelle Dillahunt** M Dillahunt **Date:** 6/5/03

Team Leader: **Lillie Golson** L Golson **Date:** 6/5/03

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cc: ANDA: 76-122
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Review

APPEARS THIS WAY
ON ORIGINAL

TENTATIVE APPROVAL SUMMARY
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: **76-122** Date of Submission: **October 25, 2001**

Applicant's Name: **Mylan Pharmaceuticals Inc.**

Established Name: **Mirtazapine Tablets, 15 mg, 30 mg, and 45 mg**

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):
Do you have 12 Final Printed Labels and Labeling? No - TENTATIVE APPROVAL
Container Labels: 30s, 100s (all 3 strengths) and 500s (45 mg)
Satisfactory in draft as of June 29, 2001 submission.
Professional Package Insert Labeling:
Satisfactory in draft as of October 25, 2001 submission.
Revisions needed post-approval: None
BASIS OF APPROVAL:
Was this approval based upon a petition? No
What is the RLD on the 356(h) form: Remeron® Tablets
NDA Number: 20-415
NDA Drug Name: Remeron® (mirtazapine) Tablets
NDA Firm: Organon
Date of Approval of NDA Insert and supplement #: 8/30/00 (S-006)
Has this been verified by the MIS system for the NDA? Yes
Was this approval based upon an OGD labeling guidance? No
Basis of Approval for the Container Labels: side-by-sides
Other Comments:

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured.		X	
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?		X	
Error Prevention Analysis			
Has the firm proposed a proprietary name? No.		X	
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.	X		
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			X
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	
Labeling			

Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?		X	
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		X	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		X	
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?		X	
Has the firm failed to describe the scoring in the HOW SUPPLIED section? THEY HAVE STATED THAT THE 15 mg and the 30 mg are scored but they have not stated that the 45 mg are unscored		X	
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		X	
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)		X	
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Because of proposed packaging configuration or for any other reason, does this applicant meet fail to meet all of the unprotected conditions of use of referenced by the RLD?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?			X
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		X	
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		X	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?	X		
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.			

FOR THE RECORD: (portions taken from previous review)

1. Review based on the labeling of Remeron®, revised 3/99; approved 8/30/00.

2. Patent/Exclusivities:

   one patent – 5977099 – 6/16/17
   no exclusivities
   The firm has filed a Paragraph IV certification to the patent.

3. Mylan is the manufacturer (p 2995 v 1.1).

4. The drug product will be made available in container sizes of 30s (CRC) and 100s (CRC) [all 3 strengths and 500s (non-CRC) [45 mg].

5. The inactives are accurately listed in the DESCRIPTION section.

6. The tablet descriptions are accurate as seen in the HOW SUPPLIED section.

7. Storage Conditions:
NDA – Store at controlled room temperature 20°-25°C (68°-77°F).
ANDA – Store at controlled room temperature 15° to 30°C (59° to 86°F)(see USP). PROTECT FROM LIGHT AND MOISTURE.
USP – not USP

8. Dispensing Recommendations:
NDA – Dispense in a tight, light-resistant container as described in the USP.
ANDA – Dispense in a tight, light-resistant container as defined by the USP using a child-resistant closure.
USP – not USP

9. Scoring:
NDA – 15 mg and 30 mg – scored --- 45 mg - unscored
ANDA - same as NDA

Date of Review: **11-6-01** **Date of Submission:** **10-25-01**

Primary Reviewer: **Adolph Vezza** **Date:** 11/7/01

A. Vezza

Team Leader: **Charlie Hoppes** **Date:** 11/7/01

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cc: ANDA: 76-122
DUP/DIVISION FILE
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Review

APPEARS THIS WAY
ON ORIGINAL

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: **76-122** Date of Submission: **June 29, 2001**

Applicant's Name: **Mylan Pharmaceuticals Inc.**

Established Name: **Mirtazapine Tablets, 15 mg, 30 mg, and 45 mg**

Labeling Deficiencies:

1. GENERAL COMMENT

   Please note that some of the comments below are the same as those faxed to you on August 8, 2001.

2. CONTAINER

   We encourage you to distinguish your product strengths by boxing, contrasting colors, or some other means.

3 INSERT

   a. DESCRIPTION

      i. Revise the structural formula by substituting a "methyl" group for the "chloride" molecule.

      ii. "anhydrous lactose" rather than "

      iii. "15 mg" and "30 mg" (add a space between the number and "mg")

      iv. Add "triacetin" to the listing of inactive ingredients.

   b. ADVERSE REACTIONS

      Other Adverse Events ..., Musculoskeletal System, rare - "pathologic" rather than

   c. DOSAGE AND ADMINISTRATION

      On further consideration please revise as follows - Elderly and Patients with Renal or Hepatic Impairment, last sentence – "(see PRECAUTIONS and CLINICAL PHARMACOLOGY)' rather than as previously requested ".

   d. HOW SUPPLIED

      i. "15 mg" and "30 mg" (add a space between the number and "mg")

ii. "**STORE AT CONTROLLED ROOM** ..." rather than "

Please revise your insert labeling, as instructed above, and submit 4 draft copies for a tentative approval or 12 final printed copies for a full approval of this application. If draft labeling is provided, please be advised that you will be required to submit 12 final printed copies of all labels and labeling at least 60 days prior to full approval of this application. In addition, you should be aware that color and other features (print size, prominence, etc) in final printed labeling could be found unacceptable and that further changes might be requested prior to approval.

Prior to approval, it may be necessary to further revise your labeling subsequent to approved changes for the reference listed drug. We suggest that you routinely monitor the following website for any approved changes – http://www.fda.gov/cder/ogd/rld/labeling_review_branch.html

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

Wm Peter Rickman
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):
Do you have 12 Final Printed Labels and Labeling? Yes No If no, list why:
Container Labels: 30s, 100s (all 3 strengths) and 500s (45 mg)
Professional Package Insert Labeling:
Revisions needed post-approval:

BASIS OF APPROVAL:
Was this approval based upon a petition? No
What is the RLD on the 356(h) form: Remeron® Tablets
NDA Number: 20-415
NDA Drug Name: Remeron® (mirtazapine) Tablets
NDA Firm: Organon
Date of Approval of NDA Insert and supplement #: 8/30/00 (S-006)
Has this been verified by the MIS system for the NDA? Yes
Was this approval based upon an OGD labeling guidance? No
Basis of Approval for the Container Labels: side-by-sides
Other Comments:

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured.		X	
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?		X	
Error Prevention Analysis			
Has the firm proposed a proprietary name? No.		X	
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.	X		
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			X
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?	X		
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		X	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		X	
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?		X	
Has the firm failed to describe the scoring in the HOW SUPPLIED section? THEY HAVE STATED THAT THE 15 mg and the 30 mg are scored but they have not stated that the 45 mg are unscored		X	
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	

Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?	X		
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		X	
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)		X	
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Because of proposed packaging configuration or for any other reason, does this applicant meet fail to meet all of the unprotected conditions of use of referenced by the RLD?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?			X
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		X	
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		X	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?	X		
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.			

NOTE TO THE CHEMIST:

The firm has failed to list one of the ingredients (triacetin) of one of the Opadrys used in this drug product.

FOR THE RECORD: (portions taken from previous review)

1. Review based on the labeling of Remeron®, revised 3/99; approved 8/30/00.

2. Patent/Exclusivities:

   one patent – 5977099 – 6/16/17
   no exclusivities
   The firm has filed a Paragraph IV certification to the patent.

3. Mylan is the manufacturer (p 2995 v 1.1).

4. The drug product will be made available in container sizes of 30s (CRC) and 100s (CRC) [all 3 strengths and 500s (non-CRC) [45 mg].

5. The inactives are accurately listed in the DESCRIPTION section except the firm has failed to list "triacetin" (one of the ingredients of one of the two [redacted] used) and they have listed '[redacted] rather than "anhydrous lactose"..

6. The tablet descriptions are accurate as seen in the HOW SUPPLIED section.

7. Storage Conditions:
   NDA – Store at controlled room temperature 20°-25°C (68°-77°F).
   ANDA – Store at controlled room temperature 15° to 30°C (59° to 86°F)(see USP). PROTECT FROM LIGHT AND MOISTURE.
   USP – not USP

8. Dispensing Recommendations:
NDA – Dispense in a tight, light-resistant container as described in the USP.
ANDA – Dispense in a tight, light-resistant container as defined by the USP using a child-resistant closure.
USP – not USP

9. Scoring:
NDA – 15 mg and 30 mg – scored --- 45 mg - unscored
ANDA - same as NDA

Date of Review: 8-30-01 **Date of Submission:** 6-29-01

Primary Reviewer: Adolph Vezza **Date:** 8/30/01

A. Vezza

Team Leader: Charlie Hoppes **Date:** 8/30/01

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cc: ANDA: 76-122
DUP/DIVISION FILE
HFD-613/AVezza/CHoppes (no cc)
aev/8/30/01|V:\FIRMSAM\MYLAN\LTRS&REV\76122na2.l
Review

APPEARS THIS WAY
ON ORIGINAL

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: **76-122** Date of Submission: **February 27, 2001**

Applicant's Name: **Mylan Pharmaceuticals Inc.**

Established Name: **Mirtazapine Tablets, 45 mg**

Labeling Deficiencies:

1. GENERAL COMMENT

   Revise your storage temperature recommendations throughout your labels and labeling as follows:

   STORE AT CONTROLLED ROOM TEMPERATURE 15° TO 30°C (59° TO 86°F)(see USP).

2 CONTAINER 30s, 100s, 500s

   See GENERAL COMMENT above.

3. INSERT

   a. DESCRIPTION

      i. Revise the structural formula by substituting a "methyl" group for the " molecule.

      ii. "anhydrous lactose" rather than "

      iii. Add "triacetin" to the listing of inactive ingredients.

   b. DOSAGE AND ADMINISTRATION

      Elderly and Patients with Renal or Hepatic Impairment, last sentence – "... PHARMACOLOGY and PRECAUTIONS)."

   c. HOW SUPPLIED

      See GENERAL COMMENT (1) above.

Please revise your container labels and insert labeling, as instructed above, and submit 4 draft copies for a tentative approval or 12 final printed copies for a full approval of this application. If draft labeling is provided, please be advised that you will be required to submit 12 final printed copies of all labels and labeling at least 60 days prior to full approval of this application. In addition, you should be aware that color and other features (print size, prominence, etc) in final printed labeling could be found unacceptable and that further changes might be requested prior to approval.

Prior to approval, it may be necessary to further revise your labeling subsequent to approved changes for the reference listed drug. We suggest that you routinely monitor the following website for any approved changes – http://www.fda.gov/cder/ogd/rld/labeling_review_branch.html

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

Wm Peter Rickman
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):

Do you have 12 Final Printed Labels and Labeling? Yes No If no, list why:

Container Labels: 30s, 100s and 500s

Professional Package Insert Labeling:

Revisions needed post-approval:

BASIS OF APPROVAL:
Was this approval based upon a petition? No
What is the RLD on the 356(h) form: Remeron® Tablets
NDA Number: 20-415
NDA Drug Name: Remeron® (mirtazapine) Tablets
NDA Firm: Organon
Date of Approval of NDA Insert and supplement #: 8/30/00 (S-006)
Has this been verified by the MIS system for the NDA? Yes
Was this approval based upon an OGD labeling guidance? No
Basis of Approval for the Container Labels: side-by-sides
Other Comments:

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured.		X	
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?		X	
Error Prevention Analysis			
Has the firm proposed a proprietary name? No.		X	
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.	X		
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			X
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?			X
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		X	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		X	
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			

Is the scoring configuration different than the RLD?		X	
Has the firm failed to describe the scoring in the HOW SUPPLIED section? THEY HAVE STATED THAT THE 15 mg and the 30 mg are scored but they have not stated that the 45 mg are unscored		X	
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?	X		
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		X	
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)		X	
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Because of proposed packaging configuration or for any other reason, does this applicant meet fail to meet all of the unprotected conditions of use of referenced by the RLD?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?			X
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		X	
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		X	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?	X		
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.			

NOTE TO THE CHEMIST:

The firm has failed to list one of the ingredients (triacetin) of one of the ~~~ used in this drug product.

FOR THE RECORD:

1. Review based on the labeling of Remeron®, revised 3/99; approved 8/30/00.

2. Patent/Exclusivities:

   two patents – 5977099 – 6/16/17 --- 5178878
   one exclusivity – NCE – 6/14/01
   The firm has filed a Paragraph IV certification to both patents.

3. Mylan is the manufacturer (p 2995 v 1.1).

4. The drug product will be made available in container sizes of 30s (CRC) 100s (CRC) and 500s (non-CRC).

5. The inactives are accurately listed in the DESCRIPTION section except the firm has failed to list "triacetin" (one of the ingredients of one of the two ~~~ used) and they have listed ~~~ rather than "anhydrous lactose"..

6. The tablet descriptions are accurate as seen in the HOW SUPPLIED section.

7. Storage Conditions:
NDA – Store at controlled room temperature 20°-25°C (68°-77°F).
ANDA – Store at room temperature 15° to 30°C (59° to 86°F). PROTECT FROM LIGHT AND MOISTURE.
USP – not USP

8. Dispensing Recommendations:
NDA – Dispense in a tight, light-resistant container as described in the USP.
ANDA – Dispense in a tight, light-resistant container as defined by the USP using a child-resistant closure.
USP – not USP

9. Scoring:
NDA – 15 mg and 30 mg – scored --- 45 mg - unscored
ANDA - 45 mg – unscored

10. This drug product cannot meet one of the conditions of use as expressed in the DOSAGE AND ADMINISTRATION section. The usual starting dose is 15 mg daily and this drug product is a 45 mg tablet.

Date of Review: **4-3-01** **Date of Submission:** **2-27-01**

Primary Reviewer: **Adolph Vezza** **Date:**

A. Vezza 4/3/01

Team Leader: **Charlie Hoppes** **Date:**

4/3/01

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cc: ANDA: 76-122
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Review

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 76-122

CHEMISTRY REVIEW(S)

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Generic Drugs
Abbreviated New Drug Application Review

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1. **CHEMISTRY REVIEW NO.** 1

2. **ANDA #** 76-122

3. **NAME AND ADDRESS OF APPLICANT**
   Mylan Pharmaceuticals Inc.
   781 Chestnut Ridge Road
   P.O. Box 4310
   Morgantown, WV 26503-4310

4. **LEGAL BASIS FOR SUBMISSION**
   Submission is based on the reference listed drug Remeron® (NDA #20-415), manufactured by Organon, Inc.

5. **SUPPLEMENT(s)** N/A

6. **PROPRIETARY NAME** N/A

7. **NONPROPRIETARY NAME** Mirtazapine Tablets

8. **SUPPLEMENT(s) PROVIDE(s) FOR:** N/A

9. **AMENDMENTS AND OTHER DATES**
   Original Submission: February 27, 2001
   FDA Acceptable for filing: February 28, 2001
   Labeling Deficiency Letter: April 3, 2001
   Bioequivalency Deficiency Letter: May 30, 2001

10. **PHARMACOLOGICAL CATEGORY** Treatment of depression

11. **Rx or OTC** R_x

12. **RELATED DMF(s)**

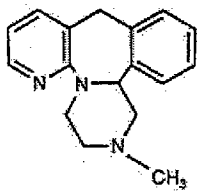
DMF #	LOA page #	Component	Manufacturer
[redacted]	2851	[redacted]	[redacted]
[redacted]	3236	[redacted]	[redacted]
[redacted]	3238	[redacted]	[redacted]
[redacted]	3240	[redacted]	[redacted]
[redacted]	3242	[redacted]	[redacted]
[redacted]	3244	[redacted]	[redacted]
[redacted]	3247	[redacted]	[redacted]
[redacted]	3250	[redacted]	[redacted]
[redacted]	3252	[redacted]	[redacted]
[redacted]	3254	[redacted]	[redacted]
[redacted]	3256	[redacted]	[redacted]

13. **DOSAGE FORM** Tablets

14. **POTENCIES** 45 mg per tablet

15. **CHEMICAL NAME AND STRUCTURE**

Mirtazapine 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:



16. **RECORDS AND REPORTS** N/A

16. **COMMENTS**: The ANDA is deficient and therefore not approvable. We have requested additional information regarding the following sections of the ANDA:

- Raw materials specifications
- Analytical methods
- Specifications for release of the drug product
- DMF

18. **CONCLUSIONS AND RECOMMENDATIONS**: Not Approvable (~~Minor~~ MAJOR Amendment) MA

19. **REVIEWER**: Susan Zuk **DATE COMPLETED**: 7/17/01

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ON ORIGINAL

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Food and Drug Administration
Center for Drug Evaluation and Research
Office of Generic Drugs
Abbreviated New Drug Application Review

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1. **CHEMISTRY REVIEW NO. 2**

2. **ANDA #** 76-122

3. **NAME AND ADDRESS OF APPLICANT**
   Mylan Pharmaceuticals Inc.
   781 Chestnut Ridge Road
   P.O. Box 4310
   Morgantown, WV 26503-4310

4. **LEGAL BASIS FOR SUBMISSION**
   Submission is based on the reference listed drug Remeron® (NDA #20-415), manufactured by Organon, Inc.

5. **SUPPLEMENT(s)** N/A

6. **PROPRIETARY NAME** N/A

7. **NONPROPRIETARY NAME** Mirtazapine Tablets

8. **SUPPLEMENT(s) PROVIDE(s) FOR:** N/A

9. **AMENDMENTS AND OTHER DATES**
   Original Submission: February 27, 2001
   Amendment to add 15 and 30 mg: June 29, 2001 *current review*
   CMC Major Amendment: October 25, 2001 *current review*

10. **PHARMACOLOGICAL CATEGORY** Treatment of depression

11. **Rx or OTC** R_x

APPEARS THIS WAY
ON ORIGINAL

12. **RELATED DMF(s)**

DMF #	LOA page #	Component	Manufacturer
[redacted]	2851	[redacted]	[redacted]

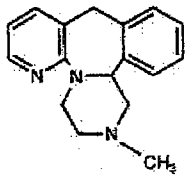
See DMF Checklist for listing of 10 Type III DMFs.

13. **DOSAGE FORM** Tablets

14. **POTENCIES** 15, 30 and 45 mg per tablet

15. **CHEMICAL NAME AND STRUCTURE**

Mirtazapine 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:



16. **RECORDS AND REPORTS** N/A

17. **COMMENTS**: The applicant has adequately responded to all other CMC deficiency comments. Refer to CMC review.

18. **CONCLUSIONS AND RECOMMENDATIONS**: Recommend Approval

Approval of ANDA 76122 is supported by the following:

- Acceptable by Bioequivalence Division 9/21/01
- Acceptable by Division of Labeling 11/7/01
- Acceptable EER Mylan 3/15/01
- Acceptable EER [redacted] 3/14/01
- DMF [redacted] Adequate 12/11/01

19. **REVIEWER**: Susan Zuk **DATE COMPLETED**: 12/11/01

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Food and Drug Administration
Center for Drug Evaluation and Research
Office of Generic Drugs
Abbreviated New Drug Application Review

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1. **CHEMISTRY REVIEW NO.** 3

2. **ANDA #** 76-122

3. **NAME AND ADDRESS OF APPLICANT**
   Mylan Pharmaceuticals Inc.
   781 Chestnut Ridge Road
   P.O. Box 4310
   Morgantown, WV 26503-4310

4. **LEGAL BASIS FOR SUBMISSION**
   Submission is based on the reference listed drug Remeron® (NDA #20-415), manufactured by Organon, Inc.

5. **SUPPLEMENT(s)** N/A

6. **PROPRIETARY NAME** N/A

7. **NONPROPRIETARY NAME** Mirtazapine Tablets

8. **SUPPLEMENT(s) PROVIDE(s) FOR:** N/A

9. **AMENDMENTS AND OTHER DATES**
   Original Submission: February 27, 2001
   Amendment to add 15 and 30 mg: June 29, 2001
   CMC Major Amendment: October 25, 2001
   Tentative Approval Granted: January 15, 2002
   Minor Amendment: January 2, 2003
   Minor Amendment: May 12, 2003

10. **PHARMACOLOGICAL CATEGORY** Treatment of depression

11. **Rx or OTC** R_x

12. **RELATED DMF(s)**

DMF #	LOA page #	Component	Manufacturer
15300	2851	Mirtazapine	Sumika Fine Chemicals Co., Ltd.

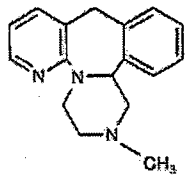
See DMF Checklist for listing of 10 Type III DMFs.

13. **DOSAGE FORM** Tablets

14. **POTENCIES** 15, 30 and 45 mg per tablet

15. **CHEMICAL NAME AND STRUCTURE**

Mirtazapine 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:



16. **RECORDS AND REPORTS** N/A

17. **COMMENTS**: The applicant requested only final approval of their 45 mg tablets in the 1/2/03 Amendment. In the subsequent 5/12/03 Amendment the firm revised their request for final approval to include the 15 mg and 30 mg tablets.

18. **CONCLUSIONS AND RECOMMENDATIONS**: Recommend Approval
The 1/2/03 amendment was submitted to notify the Agency that the court case against Mylan in regard to Mirtazapine Tablets is now closed, eliminating any legal barrier to approval of the drug product. Final approval of 15 mg, 30 mg and 45 mg tablets is recommended.

Approval of ANDA 76122 is supported by the following:

- Acceptable by Bioequivalence Division 9/21/01

- Acceptable by Division of Labeling 6/5/03
- Acceptable EER Mylan 3/15/01
- Acceptable EER [redacted] 3/14/01
- DMF [redacted]
  Adequate 2/10/03 N. Ya

19. **REVIEWER**: Susan Zuk Susan Zuk 6/10/03

DATE COMPLETED: 1/22/03, updated 6/9/03

APPEARS THIS WAY
ON ORIGINAL

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Page(s) of trade secret and /or confidential commercial information

ANDA APPROVAL SUMMARY

ANDA: 76-122

DRUG PRODUCT: Mirtazapine Tablets

FIRM: Mylan Pharmaceuticals Inc.

DOSAGE FORM: Tablets **STRENGTH:** 15, 30 and 45 mg

CGMP STATEMENT/EIR UPDATE STATUS: Signed cGMP certification was provided on page 2995 for the drug product manufacturer. An acceptable EER was issued based on profile for the drug substance manufacturer 3/14/01. An acceptable EER was issued for the drug product manufacturer 3/14/01.

BIO STUDY: The bio-study conducted on the applicant's product and Organon, Inc.'s Remeron® Tablets was found to be acceptable by the Division of Bioequivalence on 9/21/01.

METHOD VALIDATION - (DESCRIPTION OF DOSAGE FORM SAME AS FIRM'S): Both the drug substance and drug product are non-compendial. A methods validation package was sent though Diane O'Brien, MV Coordinator to the appropriate field laboratory.

STABILITY - (ARE CONTAINERS USED IN STUDY IDENTICAL TO THOSE IN CONTAINER SECTION?): Accelerated and room temperature stability data support the proposed 24 month expiration date. Containers used in the stability studies were identical to those described in the container section.

LABELING: See Approval Summary dated 6/5/03.

STERILIZATION VALIDATION (IF APPLICABLE): Not applicable to this drug product.

SIZE OF BIO BATCH (FIRM'S SOURCE OF NDS OK?): One batch of each proposed strength was manufactured by Mylan Pharmaceuticals Inc. using [redacted] by [redacted]. Batch R1H3105 (45 mg) was manufactured to a theoretical quantity of [redacted] tablets, actual packaged [redacted] tablets. Batch R1J0335 (30 mg) was manufactured to a theoretical quantity of [redacted] tablets, actual packaged [redacted] tablets. Batch R1J0334 (15 mg)

was manufactured to a theoretical quantity of [redacted] tablets, actual packaged [redacted] tablets. The executed batches were packaged in their entirety into the commercial containers. All proposed packaging systems were used. These were placed on accelerated and long-term stability study.

SIZE OF STABILITY BATCHES - (IF DIFFERENT FROM BIO BATCH, WERE THEY MANUFACTURED VIA THE SAME PROCESS?): See above.

PROPOSED PRODUCTION BATCH - (MANUFACTURING PROCESS THE SAME AS BIO/STABILITY?): The proposed production batch sizes are [redacted] tablets (45 mg), [redacted] tablets (30 mg) and [redacted] tablets (15 mg). The commercial production batch record is the identical to the exhibit batch.

Susan Zuk

CHEMIST: Susan Zuk **DATE:** 1/22/03, revised 6/9/03

SUPERVISOR: Richard Adams **DATE:**

R.C. Adams 6/10/03

APPEARS THIS WAY
ON ORIGINAL

ANDA APPROVAL SUMMARY

ANDA: 76-122

DRUG PRODUCT: Mirtazapine Tablets

FIRM: Mylan Pharmaceuticals Inc.

DOSAGE FORM: Tablets **STRENGTH:** 15, 30 and 45 mg

CGMP STATEMENT/EIR UPDATE STATUS: Signed cGMP certification was provided on page 2995 for the drug product manufacturer. An acceptable EER was issued based on profile for the drug substance manufacturer 3/14/01. An acceptable EER was issued for the drug product manufacturer 3/14/01.

BIO STUDY: The bio-study conducted on the applicant's product and Organon, Inc.'s Remeron® Tablets was found to be acceptable by the Division of Bioequivalence on 9/21/01.

METHOD VALIDATION - (DESCRIPTION OF DOSAGE FORM SAME AS FIRM'S): Both the drug substance and drug product are non-compendial. A methods validation package was sent though Diane O'Brien, MV Coordinator to the appropriate field laboratory.

STABILITY - (ARE CONTAINERS USED IN STUDY IDENTICAL TO THOSE IN CONTAINER SECTION?): Accelerated and room temperature stability data support the proposed 24 month expiration date. Containers used in the stability studies were identical to those described in the container section.

LABELING: See Approval Summary dated 6/5/03.

STERILIZATION VALIDATION (IF APPLICABLE): Not applicable to this drug product.

SIZE OF BIO BATCH (FIRM'S SOURCE OF NDS OK?): One batch of each proposed strength was manufactured by Mylan Pharmaceuticals Inc. using [redacted]. Batch R1H3105 (45 mg) was manufactured to a theoretical quantity of [redacted] tablets, actual packaged [redacted] tablets. Batch R1J0335 (30 mg) was manufactured to a theoretical quantity of [redacted] tablets, actual packaged [redacted] tablets. Batch R1J0334 (15 mg)

was manufactured to a theoretical quantity of [redacted] tablets, actual packaged [redacted] tablets. The executed batches were packaged in their entirety into the commercial containers. All proposed packaging systems were used. These were placed on accelerated and long-term stability study.

SIZE OF STABILITY BATCHES - (IF DIFFERENT FROM BIO BATCH, WERE THEY MANUFACTURED VIA THE SAME PROCESS?): See above.

PROPOSED PRODUCTION BATCH - (MANUFACTURING PROCESS THE SAME AS BIO/STABILITY?): The proposed production batch sizes are [redacted] tablets (45 mg), [redacted] tablets (30 mg) and [redacted] tablets (15 mg). The commercial production batch record is the identical to the exhibit batch.

CHEMIST: Susan Zuk **DATE:** 1/22/03, revised 6/9/03
SUPERVISOR: Richard Adams **DATE:**

R.C. Adams 6/10/03

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

76-122

BIOEQUIVALENCE REVIEW(S)

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA # : 76-122 (Amendment & Waiver) SPONSOR : Mylan Pharmaceuticals Inc.

DRUG AND DOSAGE FORM : Mirtazapine Tablets, 15 mg, 30 mg, and 45 mg

STRENGTH(S) : 15 mg, 30 mg, and 45 mg

TYPES OF STUDIES : STF X STP X MULT OTHER X

CLINICAL STUDY SITE(S) :

ANALYTICAL SITE(S) : Bioanalytical Department of Mylan Pharmaceuticals, Inc.

STUDY SUMMARY: In single-dose fasting and non-fasting BE studies, Mirtazapine Tablets, 45 mg, was shown to be bioequivalent to Remeron[R] Tablets, 45 mg. The waivers for 15 mg and 30 mg strengths are granted.

Formulation is acceptable.

DISSOLUTION : acceptable

DSI INSPECTION STATUS

Inspection needed: YES / (NO)	Inspection status:	Inspection results:
First Generic ____ New facility ____ For cause ____ other ____	Inspection requested: (date) Inspection completed: (date)	

PRIMARY REVIEWER : Carol Y. Kim BRANCH : 3

INITIAL : Carol Y. Kim DATE : 9/14/01

TEAM LEADER : Barbara M. Davit BRANCH : 3

INITIAL : BMD DATE : 9/14/01

DIRECTOR, DIVISION OF BIOEQUIVALENCE : DALE P. CONNER, Pharm. D.

for INITIAL : Nelson Salvaggio DATE : 9/21/2001

Mirtazapine Tablets, 15 mg, 30 mg, and 45 mg
ANDA 76-122
Reviewer: Carol Y. Kim
V:\firmsam\mylan\ltrs&rev\76122sta.601

Mylan Pharmaceuticals Inc.
Morgantown, WV
Submission Date: 6/13/01
~~**6/28/01**~~
6/29/01

Review of an Amendment and a Waiver Request

I. Objective

1. In a letter dated June 13, 2001, the firm submitted their responses to the Bioequivalence Deficiency letter dated May 30, 2001.

2. In a letter dated June 28, 2001, the firm requested a waiver of *in vivo* bioequivalence study requirements for two lower strength tablets, 15 mg and 30 mg, of the test product. In support of a waiver request, the firm submitted comparative dissolution data.

II. Firm's responses to Deficiency Comments

DBE's comment #1:

1. Please explain in detail the reason for the missing 8 blood samples in the fasting study and 22 blood samples from the non-fasting study. These blood samples were not received by the analytical facility. See volume 1.2, p. 461 (MIRT-00210) and volume 1.5, p. 1816 (MIRT-0021).

Firm's response #1:

Ten samples were not provided by the clinical site for the fasting study (MIRT-0020). Of the 10 samples, 2 samples (subject 21, phase I, hours 72 and 96) were from a volunteer that did not complete the biostudy. The other 8 samples were not collected due to the volunteer being absent at the sample collection time.

According to the study records, only 21 samples were not provided by the clinical site for the non-fasting study (MIRT-0021). The 21 samples were not collected due to the volunteer being absent at the sample collection time.

Reviewer's comment to firm's response #1:

The firm's response is acceptable. This reviewer confirmed that a total of 21 samples were not collected for the non-fasting study (MIRT-0021).

DBE's comment #2:

2. Please repeat dissolution testing for both test and reference products using the same batches that are used in the bioequivalence studies, applying the following testing conditions with 12 individual units:

   Apparatus: [redacted]
   Paddle Speed: [redacted]
   Medium: [redacted]
   Sampling times: 5, 10, 15, 20, and 30 minutes

   Please note that the requested medium is [redacted]

Firm's response #2:

See below for the repeated dissolution testing under the requested testing conditions.

Dissolution Data using 900 ml of 0.1 N HCl, Apparatus II, 50 RPM,

Mirtazapine Tablets, 45 mg Test Lot # R1H3105				Mirtazapine Tablets, 45 mg Reference Lot # 0109298374		
Sampling times (min)	Mean (%)	Range (%)	%CV	Mean (%)	Range (%)	%CV
5	31	[redacted]	8.1	31	[redacted]	8.2
10	83	[redacted]	6.7	77	[redacted]	9.7
15	100	[redacted]	2.0	94	[redacted]	5.2
20	101	[redacted]	1.9	99	[redacted]	1.7
30	101	[redacted]	1.5	100	[redacted]	1.3

Reviewer's comment to firm's response #2:

The firm conducted the dissolution testing using the FDA-recommended method. The dissolution data are acceptable. The dissolution data met the following specifications: NLT [redacted] (Q) of the labeled amount of mirtazapine in 15 minutes.

DBE's comment #3:

3. Please submit data to support the long-term stability of mirtazapine in frozen study samples for the period equal to the time from the first sample collection to the day the last sample was analyzed (99 days).

Firm's response #3:

Mirtazapine is stable in human plasma for at least 166 days at -70°C. This exceeds the 99 days required for MIRT-0020 and MIRT-0021 studies. See page 12 for details.

Reviewer's comment to firm's response #3:

The firm's response is acceptable. The analytical method validation report is now complete and acceptable.

DBE's comment #4:

4. Please provide the detailed SOP's for the methodology (including SOP L-301). The SOP's should include the acceptance criteria for QC samples and repeat analysis.

Firm's response #4:

The requested SOPs were submitted. See pages 14-80 for details.

Reviewer's comment to firm's response #4:

The firm's response is acceptable.

III. Request for a Wavier of *in vivo* bioequivalence study requirements

The firm submitted comparative dissolution data in support of a waiver request for two additional strength tablets, 15 mg and 30 mg, of the test product.

Apparatus and Speed: [redacted]
Volume and Medium: [redacted]

Mirtazapine Tablets, 15 mg Test Lot # R1J0334				Mirtazapine Tablets, 15 mg Reference Lot # 0869309592		
Sampling times (min)	Mean (%)	Range (%)	%CV	Mean (%)	Range (%)	%CV
5	36	[redacted]	23.8	68	[redacted]	15.1
10	88	[redacted]	16.2	94	[redacted]	7.0
15	100	[redacted]	2.5	98	[redacted]	3.2
20	101	[redacted]	2.1	100	[redacted]	1.8
30	101	[redacted]	1.6	100	[redacted]	1.5

Mirtazapine Tablets, 30 mg Test Lot # R1J0335				Mirtazapine Tablets, 30 mg Reference Lot # 0679296302		
Sampling times (min)	Mean (%)	Range (%)	%CV	Mean (%)	Range (%)	%CV
5	33	[redacted]	29.5	47	[redacted]	22.6
10	82	[redacted]	13.6	88	[redacted]	7.7
15	96	[redacted]	2.3	100	[redacted]	4.6
20	97	[redacted]	1.3	102	[redacted]	4.3
30	99	[redacted]	1.1	102	[redacted]	3.8

IV. Composition of Formulation (not to be released under FOI)

Ingredients	15 mg (mg/tab)	30 mg (mg/tab)	45 mg (mg/tab)	%
Active component				
Mirtazapine	15.0	30.0	45.0	9.65
Inactive components				
Colloidal Silicon Dioxide, NF				
Magnesium Stearate/Sodium Lauryl Sulfate (				
Anhydrous Lactose, NF (				
Microcrystalline Cellulose, NF				
Pregelatinized Starch, NF				
Croscamellose Sodium, NF				
TOTAL THEORETICAL CORE WEIGHT				
TOTAL THEORETICAL COATED WEIGHT	155.5	311.0	466.5	100.0

(1) The portion of the component does not contribute to the weight of the finished product. Therefore, quantities are expressed parenthetically. Solids contributions to the weights are listed separately.

(2) Solids consist of titanium dioxide, polydextrose. triacetin, polyethylene glycol, FD&C Yellow No. 6 Lake, and FD&C Blue No. 2 Lake. A quantitative composition statement from is provided in Section VIII.

(3) Solids consist of and polyethylene glycol.

Components and compositions of

	45 mg/tablet
Titanium dioxide	
Polydextrose	
Triacetin	
Polyethylene glycol	
FD&C Yellow No. 6 Lake	
FD&C Blue No. 2 Lake	

V. Comments

1. The single-dose bioequivalence studies, MIRT-0020 and MIRT-0021, under fasting and non-fasting conditions, conducted by Mylan Pharmaceuticals Inc. on its Mirtazapine Tablets, 45 mg, lot #R1H3105, comparing it to Remeron^{R} Tablets, 45 mg, lot #0109298374, manufactured by Organon, are found acceptable by the Division of Bioequivalence.

2. The dissolution method conducted by Mylan, on its Mirtazapine Tablets, 15 mg (lot #R1J0334), 30 mg (lot #R1J0335), and 45mg (lot #R1H3105) is acceptable.

3. The test formulation of Mirtazapine Tablets, 45 mg, was previously found acceptable by the Division of Bioequivalence (submission date 2/17/01, review date 5/18/01). The formulations of Mirtazapine Tablets, 15 mg and 30 mg, are proportionally similar to the 45 mg strength of the test product which underwent acceptable bioequivalence testing. The percent compositions of all active and inactive ingredients are the same for all test products both qualitatively and quantitatively.

4. The waivers of *in vivo* bioequivalence study requirements for the 15 mg and 30 mg strength tablets of the test product are granted based on 21 CFR 320.22 (d) (2).

5. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. Dissolution testing should be conducted in _____ using _____ The test should meet the following specification:

   Not less than ___ (Q) of the labeled amount of the drug in the dosage form is dissolved in 15 minutes.

The firm should be informed of the recommendations.

Carol Y. Kim

Carol Y. Kim, Pharm.D.
Division of Bioequivalence
Review Branch III

BRW 9/13/01

RD INITIALLED BY BDAVIT Barbara M. Davit
FT INITIALLED BY BDAVIT

Date: 9/14/01

Concur: Dale P. Conner

Date: 9/21/2001

for Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: #76-122 APPLICANT: Mylan Pharmaceuticals Inc.

DRUG PRODUCT: Mirtazapine Tablets, 15 mg, 30 mg and 45 mg

The Division of Bioequivalence has completed its review and has no further questions at this time.

The following dissolution testing should be incorporated into your stability and quality control programs:

The dissolution testing should be conducted in [redacted], using [redacted] rpm. The test should meet the following specification:

> Not less than [redacted] (Q) of the labeled amount of the drug in the dosage form is dissolved in 15 minutes.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

for Dale P. Conner, Pharm. D.
Director
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

CC: ANDA #76122
ANDA DUPLICATE
DIVISION FILE
HFD-651/ Bio Drug File
HFD-658/ Reviewer C. Kim
HFD-658/ Bio team leader B. Davit

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Endorsements: (Final with Dates)
HFD-658/ Reviewer C. Kim 9/14/01
HFD-658/ Bio team Leader B. Davit 9/14/01
HFD-650/ S. Mazzella
HFD-650/ D. Conner for 9/21/2001

BIOEQUIVALENCY - Acceptable

Submission dates: 6/13/01
and ~~6/28/01~~ ~~6/29~~ 6/29/01 (KS)

1. Study Amendment (STA)
(6/13/01)

Strengths: 45 mg

Outcome: AC

2. Waivers (WAI)
(6/28/01)

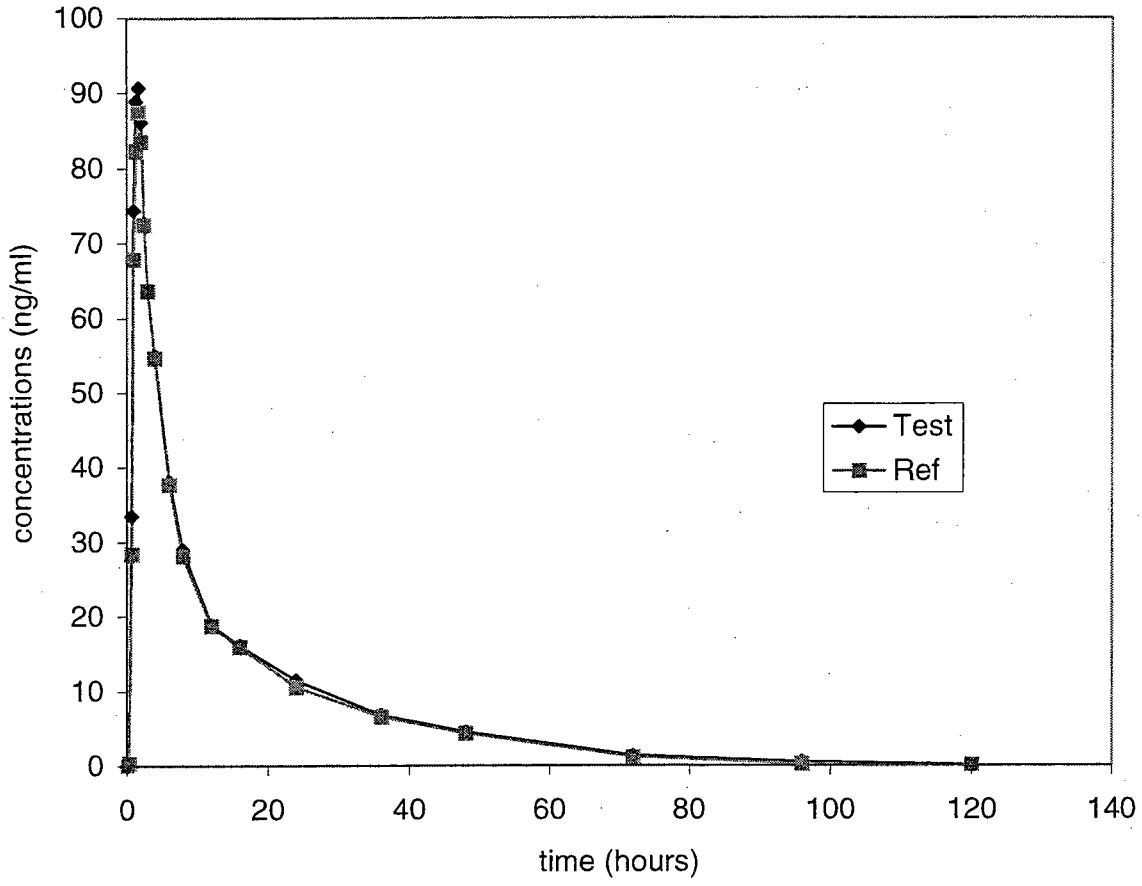
Strengths: 15 mg and 30 mg

Outcome: AC

Outcome Decision: AC - acceptable

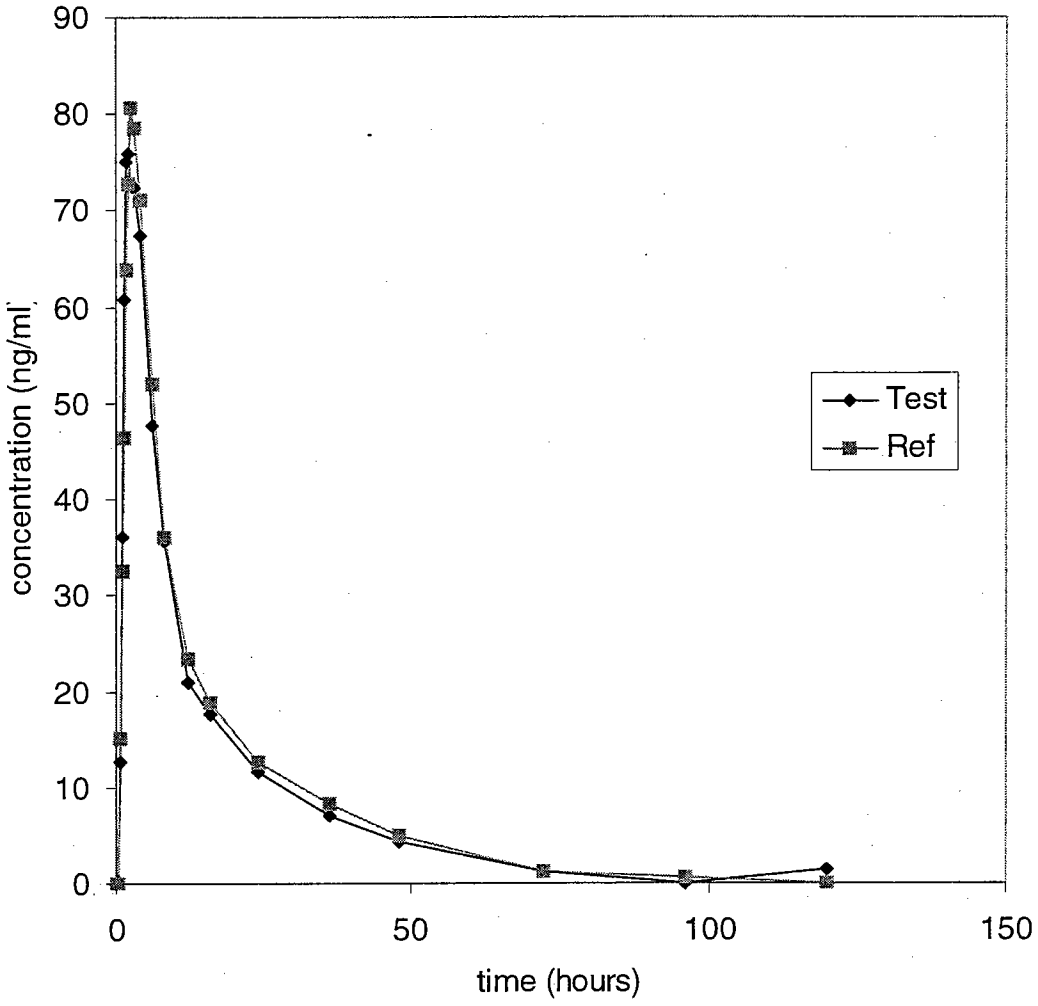
APPEARS THIS WAY
ON ORIGINAL

Fig. 1: Mean plasma concentrations under the fasting conditions, ANDA #76-122



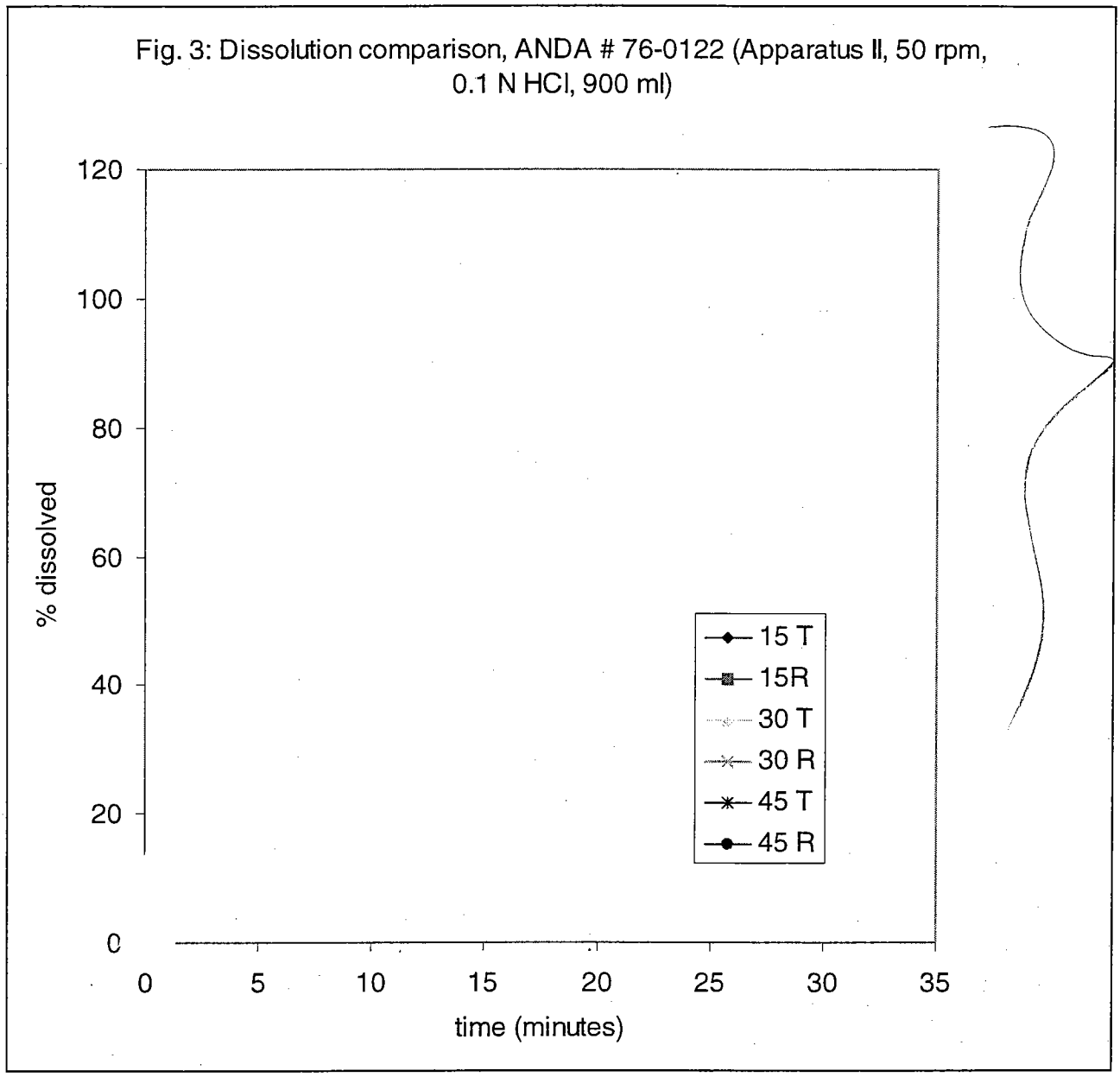
APPEARS THIS WAY
ON ORIGINAL

Fig. 2: Mean plasma concentrations under non-fasting conditions,
ANDA # 76-122



APPEARS THIS WAY
ON ORIGINAL

Fig. 3: Dissolution comparison, ANDA # 76-0122 (Apparatus II, 50 rpm, 0.1 N HCl, 900 ml)



APPEARS THIS WAY
ON ORIGINAL

Mirtazapine Tablets
45 mg
ANDA 76-122
Reviewer: Carol Y. Kim
V:\firmsam\mylan\ltrs&rev\76122sd.201

Mylan Pharmaceuticals Inc.
Morgantown, WV
Submission Date: 2/17/01

Review of Two Bioequivalence Studies and Dissolution Data (Electronic Submission)

I. Introduction

First Generic: No

Indication: For treatment of depression

Contents of Submission:

- Fasting BE: 45 mg
- Non-fasting BE: 45 mg
- *In vitro* dissolution data: 45 mg

RLD: Remeron^{R} (mirtazapine) Tablet, 15 mg, manufactured by Organon (NDA# 20415, 6/14/96)

Recommended Dose: Starting at 15 mg/day

II. Background

1. In the December 2000 Supplement to the Orange Book, the RLD was changed from Remeron^{R} Tablets, 45 mg, NDA#20415, to Remeron^{R} Tablets, 15 mg, based on OGD Associate Director for Medical Affairs' recommendation. See C#00-504 and #00-516.

2. The RLD was Remeron^{R} Tablets, 45 mg, at the time the firm conducted the bioequivalence studies. Therefore, the firm submitted the bioequivalence studies using the 45-mg strength as the RLD.

3. Only parent mirtazapine plasma concentrations and pharmacokinetic parameters were submitted for review. Since desmethylmirtazapine does not contribute meaningfully to the safety and/or efficacy of the product, PK parameters of desmethylmirtazapine were not reported. This is consistent with the recommendations in the recently-posted (10/27/00) CDER Guidance for Industry: *Bioavailability and Bioequivalence Studies for Orally-Administered Drug Products -- General Considerations.*

III. Pharmacokinetics

Mirtazapine is extensively metabolized after oral administration. Major metabolic pathways include demethylation and hydroxylation followed by glucuronide conjugation. Several cytochrome P450 isozymes are involved in the metabolism of mirtazapine. CYP2D6 and CYP1A2 catalyze the 8-hydroxylation of mirtazapine, whereas CYP3A is responsible for the formation of the N-desmethyl and N-oxide metabolite. Although several unconjugated metabolites possess pharmacological activity, they are present in the plasma at very low levels.

The mean elimination half-life of mirtazapine is approximately 20-40 hours, with a significant gender difference (mean half-life of 37 hours for females vs. 26 hours for males). Mirtazapine is approximately 85% bound to plasma proteins over a concentration range of 0.01 to 10 µg/mL.

Mirtazapine is marketed as Remeron^{R} tablets by Organon. It is available in 15 mg, 30 mg, and 45 mg tablets. The effective dose range is generally 15-45 mg/day.

IV. History of Submissions

Submission	Review completion date	Firm's name	DBE's recommendations
C00-222	8/4/00	[redacted]	Dissolution testing as the following (NDA method): Apparatus: [redacted] Speed: [redacted] Medium: [redacted] Volume: [redacted]
C00-290	8/30/00	[redacted]	1) Conduct fasting and non-fasting BE studies 2) N-demethylmirtazapine is pharmacologically active but present at very low levels in human plasma. 3) BE assessment of the drug product will be based on the plasma racemate levels of mirtazapine only.
C00-504 C00-516	1/26/01 1/26/01	[redacted]	As per Medical Officer's recommendation, the DBE changed the RLD from the 45 mg to the 15 mg tablet. The decision was based on 1) recommended starting dose is 15 mg and 2) significant adverse events.
P-00-151	2/5/01	[redacted]	1) The protocol is acceptable. 2) The waiver may be granted for 30 mg and 45 mg based on acceptable BE study on 15 mg.
C00-485	2/9/01		Dissolution testing as per NDA method

V. Study No. MIRT-0020: Randomized, 2-Way Crossover, Comparative Bioavailability Study comparing Mylan's Mirtazapine Tablets, 45 mg (1 X 45 mg), and Organon's Remeron[R] Tablets, 45 mg (1 X 45 mg), in Healthy Male Volunteers Under Fasting Conditions

Study Information

Clinical Facility:	[redacted]
Principal Investigator:	[redacted]
Clinical Study Dates:	Period I: 10/7/00-10/13/00 Period II: 10/21/00-10/27/00
Analytical Facility:	Bioanalytical Department of Mylan Pharmaceuticals Inc. Morgantown, WV
Analytical Director:	[redacted]
Analytical Study Dates:	12/19/00-1/15/01
Storage Period:	No > 99 days at -70°C

TREATMENT INFORMATION

Treatment ID:	A	B
Test or Reference:	T	R
Product Name:	Mirtazapine Tablet	Remeron[R] Tablet
Manufacturer:	Mylan	Organon
Manufacture Date:	9/15/00	N/A
Expiration Date:	-	Jan/02
ANDA Batch Size:	[redacted]	-
Full Batch Size:	[redacted]	-
Batch/Lot Number:	R1H3105	0109298374
Strength:	45 mg	45 mg
Dosage Form:	Tablet	Tablet
Dose Administered:	1 tablet (1 X 45 mg)	1 tablet (1 X 45 mg)
Study Condition:	Fasting	Fasting
Length of Fasting:	10 hours pre-dosing 4 hours post-dosing	10 hours pre-dosing 4 hours post-dosing

RANDOMIZATION		DESIGN	
Randomized:	Y	**Design Type:**	Crossover
No. of Sequences:	2	**Replicated Treatment Design:**	N
No. of Periods:	2	**Washout Period:**	14 days
No. of Treatments:	2	**Center**	single

DOSING		SUBJECTS	
Single or Multiple Dose:	single	**IRB Approval:**	Y
Steady State:	N	**Informed Consent Obtained:**	Y

Volume of Liquid Intake:	240 mL	**No. of Subjects accepted for study:**	30
Route of Administration:	oral	**No. of Subjects Completed:**	27
		No. of Subjects Plasma Analyzed:	27
		No. of Dropouts:	3
		Sex(es) Included:	Males
		Age:	19-37 years
		Healthy Volunteers Only:	Y
		No. of Adverse Events:	59

Inclusion/Exclusion Criteria:	Vol. 1.4, pp. 1118-1120
Housing:	The night before dosing until after the 24 hour post dose in each period
Blood Sampling:	0, 0.33, 0.67, 1, 1.33, 1.67, 2, 2.5, 3, 4, 6, 8, 12, 16, 24, 36, 48, 72, 96 and 120 hours post dose
Volume:	10 ml

Study Results

1) Clinical

Adverse Events: -Total- 59 adverse events in association to the study drug
-28 events (28 subjects)-treatment A related
-31 events (29 subjects)-treatment B related
-The most common adverse event was a mild drowsiness. (vol. 1.4, p. 1110)

Dropouts:

Subject #	Comments	Replacement	Excluded from the final analysis
#12	Discontinued in period I due to adverse events unrelated to the study drug	No	Yes
#13	Discontinued in period II due to vomiting (6 hours and 12 minutes post-dose)	No	Yes
#21	Failed to report for period II due to personal reasons	No	Yes

Protocol Deviations:

-Minor deviations were noted. (vol. 1.4, p.1109)

-Eight blood samples were not assayed because the samples were not provided to the analytical site from the clinical site. (vol. 1.2, p. 461)

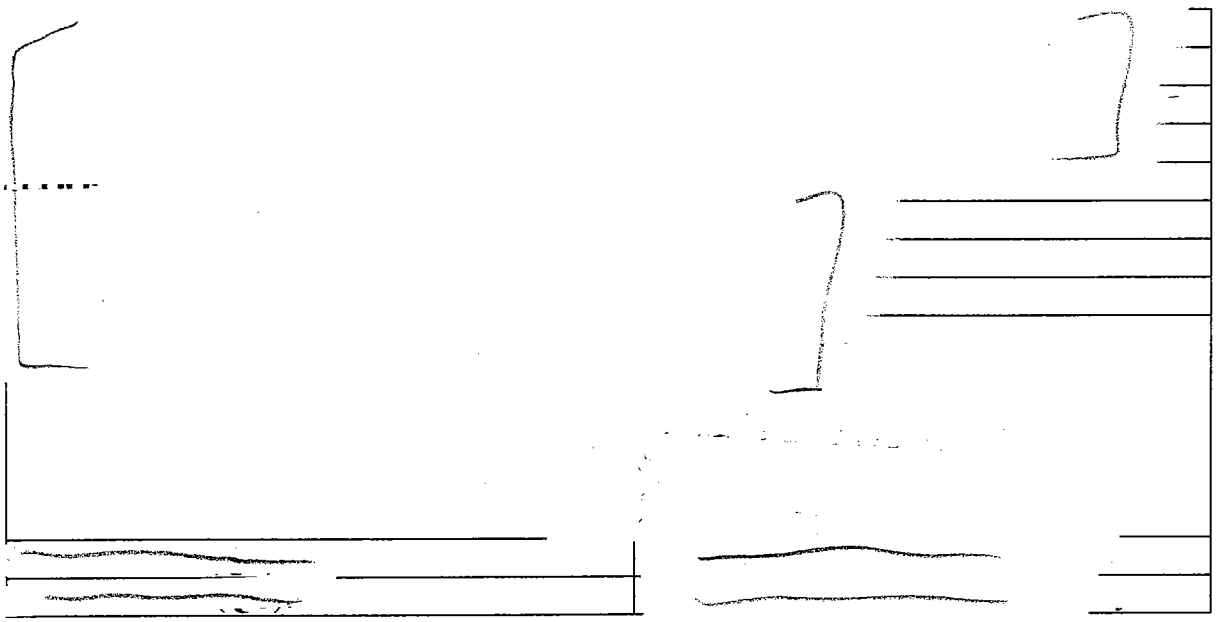
2) Analytical (Not to be Released Under FOI)

Redacted 1

Page(s) of trade secret and /or confidential commercial information

analytical

During Assay Validation



Conclusion: The analytical method is incomplete due to lack of frozen sample storage stability data.

3) Pharmacokinetic/Statistical Analysis

Mean mirtazapine plasma levels of 27 subjects are summarized in Table 1.

Table 1

Mean(%CV) Plasma Concentrations of MIRTAZAPINE
Treatment A = Mirtazapine tablets, 45 mg tablet, Dose Administered = 45 mg, fasting
Treatment B = Remeron^{R}, 45 mg tablet, Dose Administered = 45 mg, fasting

Time(hours)	Test Mean (A)	Test %CV (A)	Ref Mean (B)	Ref %CV (B)	T/R Ratio (A)/(B)
0	0.	0.	0.	0.	**
0.33	0.32	391.84	0.32	362.48	1.02
0.67	33.48	102.01	28.40	108.78	1.18
1	74.31	49.59	67.85	61.26	1.10
1.33	88.88	40.61	82.27	35.81	1.08
1.67	90.70	37.44	87.49	21.64	1.04
2	86.15	32.00	83.56	25.01	1.03
2.5	72.68	29.13	72.42	30.56	1.00
3	63.72	29.52	63.58	29.64	1.00
4	54.95	25.56	54.67	29.96	1.01
6	38.16	25.09	37.71	25.44	1.01

8	29.02	26.62	28.13	31.63	1.03
12	18.88	28.88	18.74	31.27	1.01
16	16.09	26.28	15.91	31.96	1.01
24	11.48	47.33	10.56	33.85	1.09
36	6.83	39.76	6.57	34.40	1.04
48	4.49	52.58	4.32	45.32	1.04
72	1.34	148.82	1.20	150.72	1.11
96	0.53	243.04	0.28	354.49	1.92
120	0.11	509.90	0.10	509.90	1.03

Analysis of variance was performed on each pharmacokinetic parameter using SAS PROC GLM. Mean reported pharmacokinetic parameters for mirtazapine are shown in Table 2. The Geometric means of the ln-transformed pharmacokinetic parameters, means, and the 90% confidence intervals of test product versus reference product are presented in Table 3.

Table 2

MEAN (%CV) MIRTAZAPINE PHARMACOKINETIC PARAMETERS IN TWENTY-SEVEN HEALTHY SUBJECTS FOLLOWING A SINGLE ORAL 45 MG (1 x 45 MG) DOSE OF MIRTAZAPINE TABLETS UNDER FASTING CONDITIONS

(PROTOCOL MIRT-0020)

Parameter	Arithmetic Mean A = Mylan	Arithmetic Mean B = Remeron®	LSMEANS* Ratio (A/B)
AUCL (ng x hr/mL)	919.5 (33.66)	878.9 (32.11)	1.04
AUCI (ng x hr/mL)	1027 (33.01)	988.0 (30.89)	1.03
CPEAK (ng/mL)	103.1 (33.58)	102.8 (25.70)	0.98
KEL (hr^{-1})	0.0366 (37.15)	0.0364 (33.10)	-----
HALF (hr)	22.28 (47.44)	21.62 (42.66)	-----
TPEAK (hr)	1.604 (26.95)	1.531 (31.41)	-----

* Ratio (A/B) = $e^{[\text{LSMEAN of LNA} - \text{LSMEAN of LNB}]}$

Table 3

Geometric Mean ratios and 90% confidence intervals for mirtazapine

	Geometric Means		Geometric Mean	90%CI	
Parameter*	Test	Reference	Ratio (T/R)	Lower 90% CI	Upper 90% CI
LAUC0-inf	980.1	949.2	1.03	96	111
LAUC0-t	875.0	841.6	1.04	97	112
LCmax	97.8	99.7	0.98	88	110

*LAUC0-inf =ng*hr/ml, LAUC0-t=ng*hr/ml, LCMAX=ng/ml

Comments:

1. No significant period, treatment or sequence effect for mirtazapine was noted on LAUCT, LAUCI and LCMAX ($p>0.05$).

2. The pharmacokinetic parameters and 90% confidence intervals re-calculated by the reviewer were in good agreement with the values determined by the firm.

3. The mean (%CV) AUC_T/AUC_I ratios of mirtazapine were 0.89 (4.5), range 0.78 to 0.96 and 0.89 (3.8), range 0.77 to 0.95, for test and reference, respectively.

4. The 90% confidence intervals of ln-transformed AUCT, AUCI, and CMAX for mirtazapine are all within 80-125% range.

Conclusion: The study is incomplete due to lack of frozen sample storage stability data. The firm should explain the reason for not supplying 8 blood samples to the analytical site.

VI. Study No. MIRT-0021: Randomized, 3-way crossover, comparative bioavailability study of Mylan's Mirtazapine Tablets, 45 mg (1 X 45 mg) and Organon's Remeron^R Tablets, 45 mg (1 X 45 mg), in healthy adult males under fasting & fed conditions

Study Information

Clinical Facility:	[redacted]
Principal Investigator:	[redacted]
Clinical Study Dates:	Period I: 10/30/00-11/5/00 Period II: 11/13/00-11/19/00 Period III: 11/27/00-12/3/00
Analytical Facility:	Bioanalytical Department of Mylan Pharmaceuticals Inc. Morgantown, WV
Analytical Director:	[redacted]
Analytical Study Dates:	1/3/01-1/15/01
Storage Period:	No > 76 days at -70°C

TREATMENT INFORMATION

Treatment ID:	A	B	C
Test or Reference:	T	R	R
Product Name:	Mirtazapine Tablet	Remeron^R Tablet	Mirtazapine Tablet
Manufacturer:	Mylan	Organon	Mylan
Manufacture Date:	9/15/00	-	9/15/00
Expiration Date:	-	Jan/02	-
Batch/Lot Number:	R1H3105	0109298374	R1H3105
Strength:	45 mg	45 mg	45 mg

Dosage Form:	Tablet	Tablet	Tablet
Dose Administered:	1 tablet (1 X 45 mg)	1 tablet (1 X 45 mg)	1 tablet (1 X 45 mg)
Study Condition:	Fed	Fed	Fasting
Food-drug interval	30 minutes	30 minutes	N/A
Length of Fasting:	Overnight pre-dosing	Overnight pre-dosing	Overnight pre-dosing 4 hours post-dosing
Standardized Breakfast^:	Y	Y	N

^Standardized Breakfast: 1 egg (fried), 1 buttered English muffin, 1 slice of American cheese, 1 slice of Canadian bacon, 1 serving of hash brown potatoes, 8 fluid ounces of whole milk, and 6 fluid ounces of orange juice.

RANDOMIZATION		DESIGN	
Randomized:	Y	**Design Type:**	crossover
No. of Sequences:	6	**Replicated Treatment Design:**	N
No. of Periods:	3	**Washout Period:**	14 days
No. of Treatments:	3		

DOSING		SUBJECTS	
Single or Multiple Dose:	single	**IRB Approval:**	Y
Steady State:	N	**Informed Consent Obtained:**	Y
Volume of Liquid Intake:	240 mL	**No. of Subjects Enrolled:**	22
Route of Administration:	oral	**No. of Subjects Completing:**	22
		No. of Subjects Plasma Analyzed:	22
		No. of Dropouts:	none
		Age:	18-45 years
		Sex(es) Included:	Male
		Healthy Volunteers Only:	Y
		No. of Adverse Events:	69

Inclusion/Exclusion Criteria:	Vol. 1.6, pp. 2368-2370
Housing:	The night before dosing until after the 24 hour post dose in each period
Blood Sampling:	0, 0.33, 0.67, 1, 1.33, 1.67, 2, 2.5, 3, 4, 6, 8, 12, 16, 24, 36, 48, 72, 96 and 120 hours post dose
Volume:	10 ml

Study Results

1) Clinical

Adverse Events: -Total- 69 adverse events in association to the study drug
-22 events (22 subjects)-treatment A, drug related
-24 events (22 subjects)-treatment B, drug related

-23 events (22 subjects)-treatment C, drug related
-The most common adverse event was drowsiness. (vol. 1.6, pp.2360-2361)

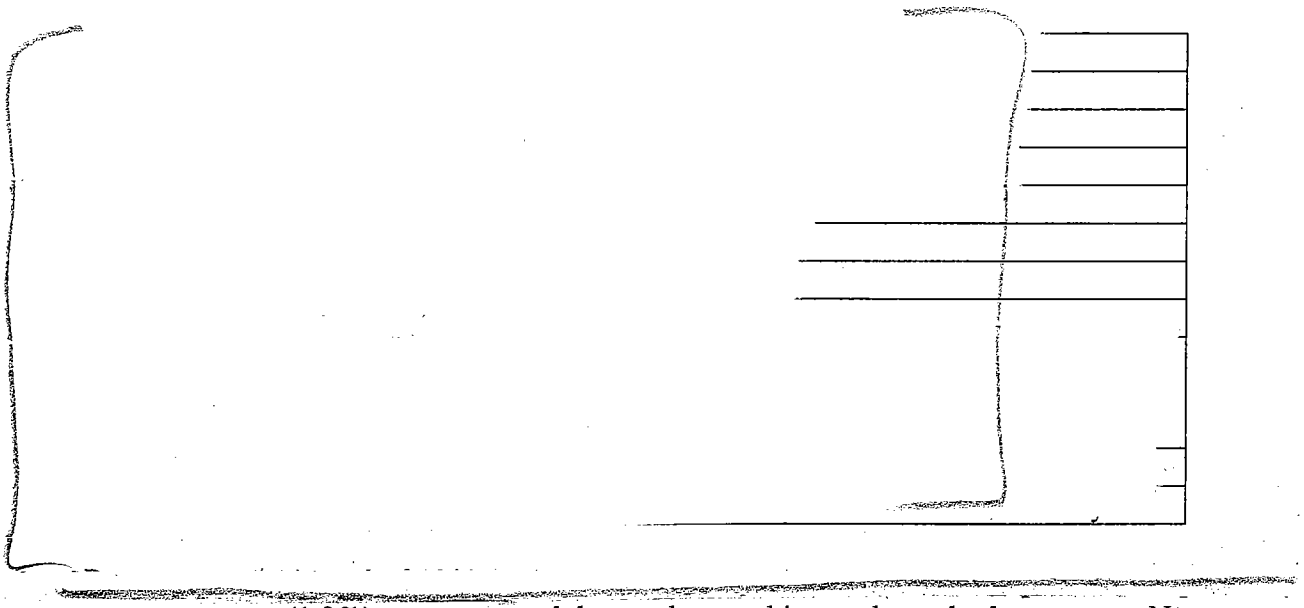
Dropout: none

Protocol Deviations:

-Minor sampling deviations were noted.
-Twenty-two blood samples were not assayed because the samples were not provided to the analytical site from the clinical site. (vol. 1.5, p. 1816)

2) Analytical (Not to be Released Under FOI)

Pre-Study Assay Validation: same as reported under fasting study



(1.9%) were repeated due to abnormal internal standard response. None were repeated for PK reasons.

3) Pharmacokinetics/Statistical Analysis

Mean plasma levels of 22 subjects are summarized in Table 4.

Table 4

Mean(%CV) Plasma Concentrations of MIRTAZAPINE
Treatment A = Mirtazapine tablets, 45 mg tablet, Dose Administered = 45 mg, fed
Treatment B = Remeron^{R}, 45 mg tablet, Dose Administered = 45 mg, fed
Treatment C = Mirtazapine tablets, 45 mg tablet, Dose Administered = 45 mg, fasting

Time(hours)	Test Mean	Test %CV	Ref Mean	Ref %CV	T/R Ratio
	(A)	(A)	(B)	(B)	(A)/(B)
0	0.	0.	0.	0.	**
0.33	0.13	469.04	0.00	0.00	**
0.67	12.75	163.70	15.13	242.48	0.84
1	36.00	110.45	32.54	148.10	1.11
1.33	60.75	64.70	46.50	87.88	1.31
1.67	75.00	49.02	63.95	59.68	1.17
2	75.94	40.88	72.88	58.18	1.04
2.5	72.74	31.31	80.57	40.67	0.90
3	72.35	20.14	78.64	27.83	0.92
4	67.37	21.14	71.19	19.72	0.95
6	47.68	25.48	52.05	26.26	0.92
8	35.68	28.98	36.08	30.89	0.99
12	21.01	27.77	23.37	29.05	0.90
16	17.59	30.83	18.86	32.68	0.93
24	11.54	32.13	12.69	39.47	0.91
36	6.96	37.30	8.23	44.04	0.85
48	4.39	58.19	4.89	69.79	0.90
72	1.17	172.38	1.16	197.12	1.01
96	0.00	0.00	0.63	239.04	0.00
120	1.38	447.21	0.00	0.00	**

Analysis of variance was performed on each pharmacokinetic parameter using SAS PROC GLM. Mean reported pharmacokinetic parameters for mirtazapine are shown in Table 5.

Table 5

MEAN (%CV) MIRTAZAPINE PHARMACOKINETIC PARAMETERS IN TWENTY-TWO HEALTHY SUBJECTS FOLLOWING A SINGLE ORAL 45 MG (1 x 45 MG) DOSE OF MIRTAZAPINE TABLETS IN A FOOD STUDY

Protocol MIRT-0021

Parameter	Arithmetic Mean A = Mylan (Fed)	Arithmetic Mean B = Remeron® (Fed)	Arithmetic Mean C = Mylan (Fasting)	*Geometric means Ratio (A/B)
AUCL (ng x hr/mL)	949.4 (27.27)	997.7 (32.83)	957.4 (36.58)	0.95
AUCI (ng x hr/mL)	1063 (30.27)	1131 (34.97)	1060 (37.41)	0.93
CPEAK (ng/mL)	97.25 (23.73)	106.5 (35.20)	124.2 (25.58)	0.95
KEL (hr^{-1})	0.0406 (38.21)	0.0414 (40.29)	0.0399 (36.76)	-----
HALF (hr)	19.92 (43.32)	19.50 (42.51)	20.63 (49.49)	-----

TPEAK (hr)	2.409 (39.01)	2.773 (50.28)	1.257 (25.81)	-----

*used natural log transformed parameter

AUCT/AUCI ratios: Test fed (A): mean 0.89, %CV 4.8%, range 0.78 to 0.95
(mirtazapine) Ref fed (B): mean 0.89, %CV 4.6%, range 0.77 to 0.93
Test fasted (C): mean 0.90, %CV 3.2% , range 0.84 to 0.95

Table 6: Root Mean Square Error (MSE) for ln-transformed AUCT and Cmax

mirtazapine	Fasting (45 mg)		Fed (45 mg)	
	ln AUCT	ln CMAX	ln AUCT	ln CMAX
MSE, Test & Reference	0.1576062	0.2367109	0.1311756	0.2594956

Comments:

1. There was no statistically significant period or sequence effect on LAUCT, LAUCI and LCMAX ($p>0.05$) for mirtazapine. A significant treatment effect on LCMAX ($p<0.05$) was noted. A slightly higher Cmax level was achieved under fasting conditions compared to fed conditions. The reviewer concluded that it does not effect the outcome of the study.

2. Under non-fasting conditions, for mirtazapine AUCI, AUCT, and CMAX, the ratios (A/B) of the geometric means are within the acceptable ranges of 0.8-1.25, respectively.

Conclusion: The study is incomplete due to lack of long term frozen stability data. The firm should explain in detail the reason for the 22 missing subject blood samples.

VII. Dissolution (Not to be released under FOI)

The firm conducted dissolution testing for Mirtazapine Tablets, 45 mg, using the following conditions:

CONDITIONS: Dissolution Medium: [redacted]
Apparatus: [redacted]
Speed: [redacted]
Sample Times: @ 10, 20 and 30 minutes
Limits: NLT [redacted] (Q) in 30 minutes

DISSOLUTION PROFILE SUMMARY

	10 MINUTES	20 MINUTES	30 MINUTES
Mylan Lot R1H3105			
Mean	88%	97%	98%
Range	[redacted]	[redacted]	[redacted]

RSD	9.1%	4.0%	3.9%
Remeron® Lot 0109298374 Mean Range RSD	63% 17.7%	90% 5.7%	96% 2.7%

Dissolution testing site: Mylan

Comments

The FDA-recommended dissolution method is different from the firm's proposed method.

FDA method
Apparatus:
Paddle speed:
Medium
Specification: NLT (Q) in 15 minutes

The firm should conduct the dissolution testing using the FDA-recommended medium, instead of

VIII. Composition of Formulation (not to be released under FOI)

COMPARATIVE QUANTITATIVE COMPOSITION
MIRTAZAPINE TABLETS, 45MG

	MG PER TABLET
ACTIVE COMPONENT	
Mirtazapine	45.0
INACTIVE COMPONENTS	
Colloidal Silicon Dioxide, NF	
Magnesium Stearate/Sodium Lauryl Sulfate	
Anhydrous Lactose, NF	
Microcrystalline Cellulose, NF	
Pregelatinized Starch, NF	
Croscamellose Sodium, NF	

TOTAL THEORETICAL CORE WEIGHT	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
TOTAL THEORETICAL COATED WEIGHT	**466.5**

(1) The [redacted] portion of the component does not contribute to the weight of the finished product. Therefore, quantities are expressed parenthetically. Solids contributions to the weights are listed separately.

(2) Solids consist of titanium dioxide, polydextrose, [redacted], triacetin, polyethylene glycol, FD&C Yellow No. 6 Lake, and FD&C Blue No. 2 Lake. A quantitative composition statement from [redacted] is provided in Section VIII.

(3) Solids consist of [redacted] and polyethylene glycol.

Components and compositions of [redacted]

[redacted]	15 mg/tablet
Titanium dioxide	[redacted]
Polydextrose	[redacted]
[redacted]	[redacted]
Triacetin	[redacted]
Polyethylene glycol	[redacted]
FD&C Yellow No. 6 Lake	[redacted]
FD&C Blue No. 2 Lake	[redacted]

At above concentrations, all inactive ingredients are within the limits specified by the FDA Inactive Ingredient Guide (1996) except for polydextrose. ANDA#74680, Ranitidine HCl Tablet, contains [redacted] of polydextrose in its approved formulation (approval dated 9/12/97). Since the content of polydextrose ([redacted]) in the proposed formulation is less than [redacted], the formulation is acceptable. (see attachment #1)

Assay and Content Uniformity

Product	Assay %	Content Uniformity(%RSD)
Test, Mrtazapine Tablets, 45 mg Lot # R1H3105	97.2	100.8 (3.6)
Reference, Remeron^{R} Tablets, 45mg Lot # 0109298374	97.9	100.2 (0.8)

IX. Comments on bioequivalence study performed on the 45 mg tablet

1. Mirtazapine exhibits linear kinetics over the dosing range of 15 to 80 mg/day. See attachment #2 for the NDA review.

2. The innovator's formulations are proportionally similar in the 15 mg, 30 mg, and 45 mg strength tablets. The 45 mg strength tablet was approved based on *in vitro* dissolution testing and the formulation proportionality. See attachment #3 for the composition of innovator's formulations.

3. The recommended starting dose for Remeron^{R} Tablet is 15 mg/day given preferably at bedtime.

4. Although none of the reported adverse events from the bioequivalence studies, MIRT-0020 and MIRT-0021, were considered severe, a significant number of subjects experienced mild drowsiness (47/59 fasting; 65/69 non-fasting). See attachment #4 for detail.

5. Therefore, the DBE currently requests conducting bioequivalence studies on the 15 mg tablet to minimize potential harm in normal or healthy volunteers.

X. Deficiency Comments

1. The firm should explain in detail the reason for the missing 8 blood samples in the fasting study and 22 blood samples from the non-fasting study. These samples were not received by the analytical facility. See volume 1.2, p. 461 (MIRT-00210) and volume 1.5, p. 1816 (MIRT-0021).

2. The firm should repeat dissolution testing for both test and reference products using the same batches that are used in the bioequivalence studies, applying the following testing conditions:

   Apparatus: [redacted]
   Paddle Speed: [redacted]
   Medium: [redacted]
   Sampling times: 5, 10, 15, 20, and 30 minutes

   The firm should note that the requested medium is [redacted]

3. The firm should submit data to support the long-term stability of mirtazapine in frozen study samples for the period equal to the time from the first sample collection to the day the last sample was analyzed (99 days).

4. The firm should provide the detailed SOP's for the analytical methodology (including SOP L-301). The SOP's should include the acceptance criteria for QC samples and repeat analysis.

XI. Recommendation

1. The single-dose bioequivalence studies, MIRT-0020 and MIRT-0021, under fasting and non-fasting conditions, conducted by Mylan Pharmaceuticals, Inc., on its Mirtazapine Tablets, 45 mg, lot #R1H3105, comparing it to Remeron^{R} Tablets, 45 mg, lot #0109298374, manufactured by Organon have been found incomplete by the Division of Bioequivalence for the reasons given in the deficiency comments.

The firm should be informed of the deficiency comments and recommendation.

Carol Y. Kim, Pharm.D.
Division of Bioequivalence
Review Branch III

5/2/01

RD INITIALLED BY BDAVIT
FT INITIALLED BY BDAVIT Barbara M Davit Date: 5/4/01

Concur: Dale P. Conner Date: 5/18/2001

Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence

APPEARS THIS WAY
ON ORIGINAL

BIOEQUIVALENCY DEFICIENCIES

ANDA: #76-122 APPLICANT: Mylan Pharmaceuticals, Inc.

DRUG PRODUCT: Mirtazapine Tablets, 45 mg

The Division of Bioequivalence has completed its review. The following deficiencies have been identified:

1. Please explain in detail the reason for the missing 8 blood samples in the fasting study and 22 blood samples from the non-fasting study. These blood samples were not received by the analytical facility. See volume 1.2, p. 461 (MIRT-00210) and volume 1.5, p. 1816 (MIRT-0021).

2. Please repeat dissolution testing for both test and reference products using the same batches that are used in the bioequivalence studies, applying the following testing conditions with 12 individual units:

   Apparatus: [redacted]
   Paddle Speed: [redacted]
   Medium: [redacted]
   Sampling times: 5, 10, 15, 20, and 30 minutes

   Please note that the requested medium is 0.1 N HCl.

3. Please submit data to support the long-term stability of mirtazapine in frozen study samples for the period equal to the time from the first sample collection to the day the last sample was analyzed (99 days).

4. Please provide the detailed SOP's for the methodology (including SOP L-301). The SOP's should include the acceptance criteria for QC samples and repeat analysis.

Sincerely yours,

for Dale P. Conner, Pharm. D.
Director
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

CC: ANDA #76-122
ANDA DUPLICATE
DIVISION FILE
HFD-651/ Bio Drug File
HFD-658/ Reviewer C. Kim
HFD-658/ Bio team leader B. Davit

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Endorsements: (Final with Dates)
HFD-658/ Reviewer C. Kim 5/4/01
HFD-658/ Bio team Leader B. Davit 5/4/01
HFD-650/ S. Mazzella
HFD-650/ D. Conner for 5/18/2001

BIOEQUIVALENCY - Incomplete Submission date: 2/27/01

1. Fasting Study (STF) **Strength: 45 mg**
Clinical: [redacted] **Outcome: IC**
Analytical: Bioanalytical Dept. of Maylan Pharmaceuticals Inc.

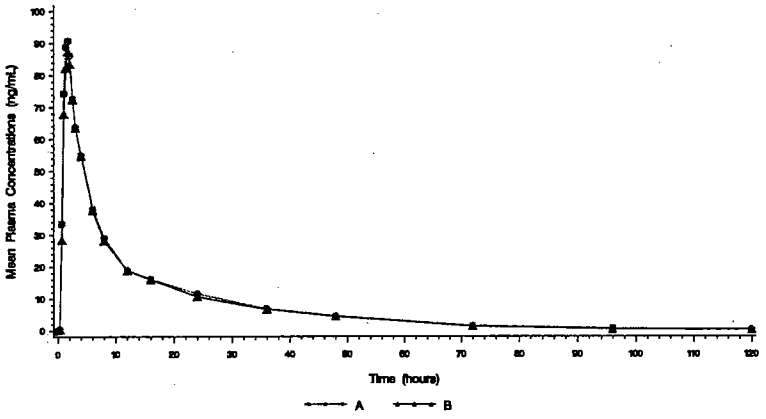
2. Fed Study (STD) **Strength: 45 mg**
Clinical: [redacted] **Outcome: IC**
Analytical: Bioanalytical Dept. of Maylan Pharmaceuticals Inc.

Outcome Decisions: IC - incomplete

APPEARS THIS WAY
ON ORIGINAL

FIGURE 1

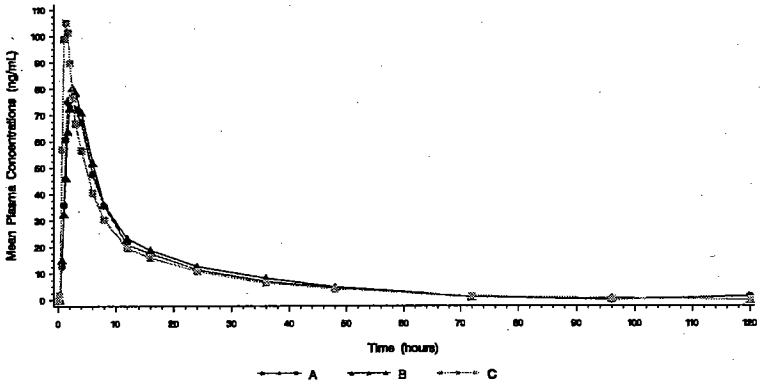
MIRTAZAPINE (MIRT – 0020)
Total Dose: 45 mg (1x45mg Tablets), Study Type: Fasting
Mean Mirtazapine Plasma Concentrations
N=27



Treatment A is A (Mirtazapine #R1H3105)
Treatment B is B (Remeron #0109298374)

FIGURE 2

MIRTAZAPINE (MIRT – 0021)
Total Dose: 45 mg (1x45mg Tablets), Study Type: Fed
Mean Mirtazapine Plasma Concentrations
N=22



Treatment A is A (Mirtazapine #R1H3105 – –fed)
Treatment B is B (Remeron #0109298374 – –fed)
Treatment C is C (Mirtazapine #R1H3105 – –fast)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

76-122

CORRESPONDENCE

MYLAN PHARMACEUTICALS INC
781 Chestnut Ridge Road • P. O. Box 4310 • Morgantown, West Virginia 26504-4310 U.S.A. • (304) 599-2595

May 27, 2003

TELEPHONE AMENDMENT
(LABELING INFORMATION ENCLOSED)

Office of Generic Drugs, CDER, FDA
Gary J. Buehler, Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

[illegible] AMENDMENT
N/AF

RE: MIRTAZAPINE TABLETS, 15MG, 30MG AND 45MG
ANDA 76-122
(Response to FDA Telephone Call Received May 27, 2003)

Dear Mr. Buehler:

Reference is made to the above referenced Abbreviated New Drug Application which was granted Tentative Approval on January 15, 2002. Reference is also made to our Minor Amendments submitted on January 2, 2003 and May 12, 2003 in which we requested final approval for the 45mg tablet strength of Mirtazapine Tablets and the 15mg and 30mg tablet strengths of Mirtazapine Tablets, respectively. On May 16, 2003, we provided Final Printed Labeling of our outsert which included all three product strengths of Mirtazapine Tablets, 15mg, 30mg and 45mg, in a single product outsert.

Reference is also made to a telephone call received on May 27, 2003 from Ms. Michelle Dillahunt, of your office, regarding the clarity of our Final Printed Bottle Labels for the 15mg and 30mg tablet strengths included in our May 12, 2003 Minor Amendment. As requested by Ms. Dillahunt, Attachment 1 contains 12 (twelve) copies of the following final printed bottle labels for Mylan's Mirtazapine Tablets, 15mg and 30 mg:

15mg
Code RM3515H - Bottles of 30 Tablets
Code RM3515A - Bottles of 100 Tablets

30mg
Code RM3530H - Bottles of 30 Tablets
Code RM3530A - Bottles of 100 Tablets

Please note that our Final Printed Bottle Labels for the 45mg tablet strength remains the same as those submitted on January 2, 2003.

As requested by Ms. Dillahunt, Mylan commits to update our storage statement on the product outsert and bottle labels prior to launch to state "Store at 20° to 25°C (68° to 77°F). [See USP for Controlled Room Temperature]. The labeling incorporating the revised storage statement will be submitted in the first post approval Annual Report.

Department—Fax Numbers		Information Systems	(304) 285-6404	Purchasing	(304) 598-5401
Accounting	(304) 285-6403	Label Control	(800) 848-0463	Quality Assurance	(304) 598-5407
Administration	(304) 599-7284	Legal Services	(304) 598-5408	Quality Control	(304) 598-5409
Business Development	(304) 598-5419	Maintenance & Engineering	(304) 598-5411	Regulatory Affairs	(304) 285-6407
Corporate Services	(304) 598-5404	Medical Unit	(304) 598-5445	Research & Development	(304) 285-6409
Human Resources	(304) 598-5406	Product Development	(304) 285-6411	Sales & Marketing	(304) 598-3232

This amendment is submitted in duplicate. Should you require additional information or have any questions regarding this amendment, please contact the undersigned at (304) 599-2595, ext. 6551 or via facsimile at (304) 285-6407.

Sincerely,

S. Wayne Talton
Executive Director
Regulatory Affairs

SWT/dmy

Desk Copy: Ms. Michelle Dillahunt, Division of Labeling and Program Support

Enclosure

APPEARS THIS WAY
ON ORIGINAL

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MYLAN PHARMACEUTICALS INC
781 Chestnut Ridge Road • P. O. Box 4310 • Morgantown, West Virginia 26504-4310 U.S.A. • (304) 599-2595

May 16, 2003

AMENDMENT
(LABELING INFORMATION ENCLOSED)

Office of Generic Drugs, CDER, FDA
Gary J. Buehler, Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ORIG AMENDMENT
N/AF

FPL

RE: MIRTAZAPINE TABLETS, 15MG, 30MG AND 45MG
ANDA 76-122

Dear Mr. Buehler:

Reference is made to the above referenced Abbreviated New Drug Application which was granted Tentative Approval on January 15, 2002. Reference is also made to our Minor Amendments submitted on January 2, 2003 and May 12, 2003 in which we requested final approval for the 45mg tablet strength of Mirtazapine Tablets and the 15mg and 30mg tablet strengths of Mirtazapine Tablets, respectively.

Per our conversation with the Office on May 15, 2003, we wish to amend our May 12, 2003 Minor Amendment to provide Final Printed Labeling of our outsert which has been revised to include all three product strengths of Mirtazapine Tablets (15mg, 30mg and 45mg) in a single outsert. Please note that our Final Printed Bottle Labels remain the same as those submitted on January 2, 2003 (for the 45mg tablet strength) and those submitted on May 12, 2003 (for the 15mg and 30mg tablet strengths).

Enclosed in Attachment 2 are twelve (12) copies of the revised final printed outsert (Code MTZP:R4; REVISED MAY 2003) for Mylan's Mirtazapine Tablets, 15mg, 30mg and 45mg.

To facilitate review of this labeling, Attachment 1 contains a side-by-side comparison of Mylan's revised final printed outsert (MTZP:R4; REVISED MAY 2003) to Mylan's previously submitted outsert (MTZP:R3; REVISED MAY 2003).

This amendment is submitted in duplicate. Should you require additional information or have any questions regarding this amendment, please contact the undersigned at (304) 599-2595, ext. 6551 or via facsimile at (304) 285-6407.

Sincerely,

S. Wayne Talton
Executive Director
Regulatory Affairs

SWT/ems

Enclosure

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MAY 19 2003
OGD / CDER

Department—Fax Numbers					
Accounting	(304) 285-6403	Information Systems	(304) 285-6404	Purchasing	(304) 598-5401
Administration	(304) 599-7284	Label Control	(800) 848-0463	Quality Assurance	(304) 598-5407
Business Development	(304) 598-5419	Legal Services	(304) 598-5408	Quality Control	(304) 598-5409
Corporate Services	(304) 598-5404	Maintenance & Engineering	(304) 598-5411	Regulatory Affairs	(304) 285-6407
Human Resources	(304) 598-5406	Medical Unit	(304) 598-5445	Research & Development	(304) 285-6409
		Product Development	(304) 285-6411	Sales & Marketing	(304) 598-3232

MYLAN PHARMACEUTICALS INC
781 Chestnut Ridge Road • P. O. Box 4310 • Morgantown, West Virginia 26504-4310 U.S.A. • (304) 599-2595

NEW CORRESP
NC

May 13, 2003

GRATUITOUS AMENDMENT

Office of Generic Drugs, CDER, FDA
Gary J. Buehler, Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: MIRTAZAPINE TABLETS, 15MG, 30MG AND 45MG
ANDA 76-122

Dear Mr. Buehler:

Reference is made to the above referenced Abbreviated New Drug Application and to our Minor Amendment submitted on May 12, 2003 in which we requested final approval for the 15mg and 30mg tablet strengths of Mirtazapine Tablets. The purpose of this amendment is to submit the original Patent Amendment letter which we inadvertently omitted from the May 12, 2003 submission.

This amendment is submitted in duplicate. Should you require additional information or have any questions regarding this amendment, please contact the undersigned at (304) 599-2595, ext. 6551 or via facsimile at (304) 285-6407.

Sincerely,

S. Wayne Talton
Executive Director
Regulatory Affairs

SWT/dmy

Enclosure

RECEIVED
MAY 14 2003
OGD / CDER

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Department—Fax Numbers		Information Systems	(304) 285-6404	Purchasing	(304) 598-5401
Accounting	(304) 285-6403	Label Control	(800) 848-0463	Quality Assurance	(304) 598-5407
Administration	(304) 599-7284	Legal Services	(304) 598-5408	Quality Control	(304) 598-5409
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Human Resources	(304) 598-5406	Product Development	(304) 285-6411	Sales & Marketing	(304) 598-3232

THIS APPROVAL SUPERSEDES THE TENTATIVE APPROVAL FOR THE OCTOBER 25, 2001 SUBMISSION

APPROVAL SUMMARY
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: **76-122** **Date of Submission: January 2, 2003**

Applicant's Name: **Mylan Pharmaceuticals Inc.**

Established Name: **Mirtazapine Tablets, 45 mg**

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):
Do you have 12 Final Printed Labels and Labeling? Yes
Container Labels: 30s, 100s and 500s
Satisfactory in FPL as of the January 2, 2003 submission.
Professional Package Insert Labeling:
Satisfactory in FPL as of the January 2, 2003 submission.(Vol 6.1; Rev.Dec. 2002;Code MTZP:R1)

Revisions needed post-approval: The firm needs to submit FPL for the 15 mg and the 30 mg strengths when TEVA's 180 day exclusivity expires. See FTR #3

BASIS OF APPROVAL:

Patent Data – 20-415

No	Expiration	Use Code	Use	File
5,977,099	6-16-17		Pharmaceutical composition comprising mirtazapine and one or more selective serotonin reuptake inhibitors	IV

Exclusivity Data - 20-415

Code/sup	Expiration	Use Code	Description		Labeling Impact
S-009	4-9-05	M-18	INFORMATION DENOTING THE EFFICACY OF REMERON IN MAINTAINING A RESPONSE IN PATIENTS WITH MAJOR DEPRESSIVE DISORDER (MDD)		Changes to CLINICAL PHARMACOLOGY, PRECAUTIONS and DOSAGE AND ADMINISTRATION

Was this approval based upon a petition? No
What is the RLD on the 356(h) form: Remeron® Tablets
NDA Number: 20-415
NDA Drug Name: Remeron® (mirtazapine) Tablets
NDA Firm: Organon
Date of Approval of NDA Insert and supplement #: 4/9/02 (S-009) and 9/30/02 (S-015)
Has this been verified by the MIS system for the NDA? Yes
Was this approval based upon an OGD labeling guidance? No
Basis of Approval for the Container Labels: side-by-sides
Other: This application is only approved for the 45 mg strength tablet at this time

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured.		X	
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?		X	
Error Prevention Analysis			
Has the firm proposed a proprietary name? No.		X	
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.	X		
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			X
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?		X	
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		X	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		X	
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?		X	
Has the firm failed to describe the scoring in the HOW SUPPLIED section? THEY HAVE STATED THAT THE 15 mg and the 30 mg are scored but they have not stated that the 45 mg are unscored		X	
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		X	
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)		X	
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Because of proposed packaging configuration or for any other reason, does this applicant meet fail to meet all of the unprotected conditions of use of referenced by the RLD?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?			X
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		X	
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		X	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?	X		

Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.			

FOR THE RECORD: (portions taken from previous review)

1. Review based on the labeling of Remeron® (NDA 20-415/S-009), approved 4/9/02 and S-015, approved 9/30/02.
The firm has sought pediatric exclusivity for their pediatric clinical studies, however they were denied exclusivity because of their failure to obtain longer-term safety data as required under the written request. (See file folder)

2. Patent/Exclusivities:

one patent – 5977099 – 6/16/17
M 18 exclusivity
The firm has filed a Paragraph IV certification to the patent.

Summary of labeling changes as a result of the above exclusivity:

a. CLINICAL PHARMACOLOGY

Last paragraph of section - describing a longer-term study - was carved out.

b. INDICATIONS AND USAGE (Third paragraph)

i. First sentence revised.

ii. Second sentence deleted.

iii. Last sentence revised

c. PRECAUTIONS (Use in Patients with Concomitant Illness)

Second sentence deleted.

d. ADVERSE REACTIONS

i. ECG Changes subsection revised

ii. New subsection added as last subsection.

e. DOSAGE AND ADMINISTRATION

Maintenance/Extended Treatment subsection revised.

3. Labeling

Mylan has submitted an amendment for approval of the 45 mg strength only. Mylan believes they are the first to file a paragraph IV for this strength and would be entitled to 180 day exclusivity. Teva would be eligible for 180 day exclusivity for the 15 mg and 30 mg strengths.
This approval summary is for the 45 mg strength only, Mylan needs to supplement this application when Teva's exclusivity for the 15 mg and 30 mg expires.

4. Mylan is the manufacturer (p 2995 v 1.1).

5. The drug product will be made available in container sizes of 30s (CRC),100s (CRC) and 500s (non-CRC)

6. The inactives are accurately listed in the DESCRIPTION section.

7. The tablet descriptions are accurate as seen in the HOW SUPPLIED section.

8. Storage Conditions:
NDA – Store at controlled room temperature 20°-25°C (68°-77°F).
ANDA – Store at controlled room temperature 15° to 30°C (59° to 86°F)(see USP). PROTECT FROM LIGHT AND MOISTURE.
USP – not USP

9. Dispensing Recommendations:
NDA – Dispense in a tight, light-resistant container as described in the USP.
ANDA – Dispense in a tight, light-resistant container as defined by the USP using a child-resistant closure.
USP – not USP

10. Scoring:
NDA – 45 mg - unscored
ANDA - same as NDA

Date of Review: 01-17-03 **Date of Submission:** 01-02-03

Primary Reviewer: Michelle Dillahunt MDillahunt **Date:** 1/22/03

Team Leader: Lillie Golson LGolson **Date:** 1/23/03

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cc: ANDA: 76-122
DUP/DIVISION FILE
HFD-613/MDillahunt/LGolson (no cc)
V:\FIRMSAM\MYLAN\LTRS&REV\76122AP.L45
Review

APPEARS THIS WAY
ON ORIGINAL

MYLAN PHARMACEUTICALS INC
781 Chestnut Ridge Road • P. O. Box 4310 • Morgantown, West Virginia 26504-4310 U.S.A. • (304) 599-2595

ORIG AMENDMENT
N/Am

May 12, 2003

MINOR AMENDMENT
(PATENT AMENDMENT AND REQUEST FOR FINAL APPROVAL)

Office of Generic Drugs, CDER, FDA
Gary J. Buehler, Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: MIRTAZAPINE TABLETS, 15MG, 30MG AND 45MG
ANDA 76-122

Dear Mr. Buehler:

Reference is made to the Abbreviated New Drug Application (ANDA) identified above which was granted Tentative Approval on January 15, 2002. Reference is also made to our Minor Amendment submitted on January 2, 2003 in which we requested final approval for the 45mg tablet strength. The purpose of this amendment is to request final approval from FDA for the 15mg and 30 mg tablet strengths of Mirtazapine Tablets.

The reason and rationale for Mylan's request for final approval of the 15mg and 30mg strengths of Mirtazapine Tablets is described as follows. Mylan submitted its ANDA for Mirtazapine Tablets, 45mg on February 27, 2001 and amended the application on June 29, 2001 to include the 15mg and 30mg strengths of this product. Both the original and amended applications included a paragraph IV patent certification. As indicated in our patent amendment submitted on January 16, 2002, litigation against Mylan was initiated by the patent and NDA holder with regard to the Paragraph IV certification. As confirmed in the documentation provided in Attachment 1 of this current amendment, a previously filed motion for summary judgment has been granted (December 18, 2002) and the case closed. Therefore, no legal barrier exists which precludes final approval of Mylan's ANDA.

The 180 day marketing exclusivity rights for the first approved generic version of 15mg and 30mg Mirtazapine Tablets (Teva Pharmacueticals) expires on June 16, 2003. As such, Mylan's ANDA is eligible to receive final approval for the 15mg and 30mg strengths on June 16, 2003. Mylan acknowledges that the 45mg strength will remain tentatively approved until the Agency has responded to the Citizen's Petition submitted by Mylan to the Agency on May 31, 2002.

As part of this request for final approval Mylan is also providing a patent amendment to address the M-18 exclusivity for the reference listed drug, Remeron®, which was recently listed in the publication entitled, "Approved Drug Products with Therapeutic Equivalence Evaluations." Mylan is not requesting approval for the information contained in the M-18 exclusivity and has, therefore, excluded this information from the proposed product labeling. The Patent Amendment is provided in Attachment 2.

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MAY 13 2003
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Department—Fax Numbers					
Accounting	(304) 285-6403	Information Systems	(304) 285-6404	Purchasing	(304) 598-5401
Administration	(304) 599-7284	Label Control	(800) 848-0463	Quality Assurance	(304) 598-5407
Business Development	(304) 598-5419	Legal Services	(304) 598-5408	Quality Control	(304) 598-5409
Corporate Services	(304) 598-5404	Maintenance & Engineering	(304) 598-5411	Regulatory Affairs	(304) 285-6407
Human Resources	(304) 598-5406	Medical Unit	(304) 598-5445	Research & Development	(304) 285-6409
		Product Development	(304) 285-6411	Sales & Marketing	(304) 598-3232

Enclosed in Attachment 6 are twelve (12) copies of the following final printed bottle labels and outsert for Mylan's Mirtazapine Tablets, 15mg and 30 mg:

BOTTLE LABELS

15mg
Code RM3515H - Bottles of 30 Tablets
Code RM3515A - Bottles of 100 Tablets

30mg
Code RM3530H - Bottles of 30 Tablets
Code RM3530A - Bottles of 100 Tablets

OUTSERT

Code MTZP:R3, Revised May 2003

Mylan's outsert has been revised to coincide with the labeling text provided in the Agency's November 6, 2002 correspondence. A copy of the Agency correspondence is provided in Attachment 3. To facilitate review of this labeling, Attachment 4 contains a side-by-side comparison of Mylan's final printed bottle labels to the draft bottle labels previously submitted. Attachment 5 contains a side-by-side comparison of Mylan's revised final printed outsert (MTZP:R3; REVISED MAY 2003) to Mylan's previously submitted outsert (MTZP:R1: REVISED DECEMBER 2002)

Except for the identified labeling revisions, this amendment provides notification that no other changes have been made to the method of manufacture for the drug product or to any other conditions outlined in the CMC section of this application since the date of tentative approval.

Pursuant to 21 CFR 314.96(b), we certify that a true copy of this amendment, as submitted to the Office of Generic Drugs, has been forwarded to the FDA's Baltimore District Office.

This amendment is submitted in duplicate. Should you require additional information or have any questions regarding this amendment, please contact the undersigned at (304) 599-2595, ext. 6551 or via facsimile at (304) 285-6407.

Sincerely,

S. Wayne Talton
Executive Director
Regulatory Affairs

SWT/dmy

Enclosure

MYLAN PHARMACEUTICALS INC
781 Chestnut Ridge Road • P. O. Box 4310 • Morgantown, West Virginia 26504-4310 U.S.A. • (304) 599-2595

January 2, 2003

ORIG AMENDMENT

N/AW

Office of Generic Drugs, CDER, FDA
Gary J. Buehler, Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

MINOR AMENDMENT
Request for Final ANDA Approval
(Patent Amendment Enclosed)

NEW CORRESP
NC

RE: MIRTAZAPINE TABLETS, 15MG, 30MG AND 45MG
ANDA 76-122

Dear Mr. Buehler:

Reference is made to the Abbreviated New Drug Application (ANDA) identified above which was granted Tentative Approval on January 15, 2002. This amendment requests final approval from FDA for the 45mg strength of Mirtazapine Tablets and acknowledges that the 15mg and 30mg strengths will remain tentatively approved.

The reason and rationale for Mylan's request for final approval of the 45mg strength of Mirtazapine Tablets is described as follows. Mylan submitted its ANDA for Mirtazapine Tablets, 45mg on February 27, 2001 and amended this application on June 29, 2001 to include the 15mg and 30mg strengths of this product. Both the original and amended applications included a paragraph IV patent certification. As indicated in our patent amendment submitted on January 16, 2002, litigation against Mylan was initiated by the patent and NDA holder with regard to the Paragraph IV certification. As confirmed in the documentation provided in Attachment 1 of this current amendment, a previously filed motion for summary judgment has recently been granted (December 18, 2002) and the case closed. Therefore, no legal barrier exists which precludes final approval of Mylan's ANDA.

Mylan is requesting final approval for the 45mg strength of Mirtazapine (ANDA 76-122) because Mylan believes it was the first company to file a substantially complete application for this product strength and is, therefore, entitled to approval and 180 days of exclusivity under the statute. The rationale for Mylan's position is described in detail in the Citizen Petition pertaining to this issue, which was submitted to the FDA on May 31, 2002. A copy of this petition, which has not yet been responded to by the Agency, is provided in Attachment 2. The basis for this petition is FDA's acceptance for filing of an incomplete ANDA submitted by Teva Pharmaceuticals. The Teva application was not substantially complete because it referenced a non-existent Drug Master File at the time of submission. The Agency should have Refused to Accept the Teva application on the grounds that it was not substantially complete. Had FDA done so, Mylan's 45mg Mirtazapine Tablets ANDA, accepted on February 28, 2001, would have been the first accepted for filing containing a Paragraph IV certification.

As Mylan amended its Mirtazapine ANDA to include the 15mg and 30mg strengths on June 29, 2001, final approval of these strengths is not being requested at this time and Mylan acknowledges that these two strengths will remain tentatively approved until the expiration of Teva's 180-day exclusivity for these two strengths and subsequent approval by the FDA.

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Department—Fax Numbers		Information Systems	(304) 285-6404	Purchasing	(304) 598-5401
Accounting	(304) 285-6403	Label Control	(800) 848-0463	Quality Assurance	(304) 598-5407
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Human Resources	(304) 598-5406	Product Development	(304) 285-6411	Sales & Marketing	(304) 598-3232

As part of this request for final approval Mylan is also providing a patent amendment to address the M-18 exclusivity for the reference listed drug, Remeron®, which was listed in Cumulative Supplement 2 (February, 2002) to the FDA's 22nd edition of the publication entitled, "Approved Drug Products with Therapeutic Equivalence Evaluations." Mylan is not requesting approval for the information contained in the M-18 exclusivity and is, therefore, excluding this information from the proposed product labeling. The Patent Amendment is provided in Attachment 3.

Enclosed in Attachment 7 are twelve (12) copies of the following final printed bottle labels and outsert for Mylan's Mirtazapine Tablets, 45mg:

BOTTLE LABELS

45mg
Code RM3545H - Bottles of 30 Tablets
Code RM3545A - Bottles of 100 Tablets
Code RM3545B - Bottles of 500 Tablets

OUTSERT

Code MTZP:R1, Revised December 2002

Mylan's outsert has been revised to coincide with the labeling text provided in the Agency's November 6, 2002 correspondence. A copy of the Agency correspondence is provided in Attachment 4. To facilitate review of this labeling, Attachment 5 contains a side-by-side comparison of Mylan's final printed bottle labels to the draft bottle labels previously submitted. Attachment 6 contains a side-by-side comparison of Mylan's final printed outsert to the outsert contained in the Agency's November 6, 2002 correspondence.

Except for the identified labeling revisions, this amendment provides notification that no other changes have been made to the method of manufacture for the drug product or to any other conditions outlined in the CMC section of this application since the date of tentative approval.

Pursuant to 21 CFR 314.96(b), we certify that a true copy of this amendment, as submitted to the Office of Generic Drugs, has been forwarded to the FDA's Baltimore District Office.

This amendment is submitted in duplicate. Should you require additional information or have any questions regarding this amendment, please contact the undersigned at (304) 599-2595, ext. 6600 or via facsimile at (304) 285-6407.

Sincerely,

Frank R. Sisto
Executive Vice President
Regulatory Affairs and Generic Drug Development

FRS/dn
Enclosure

MYLAN PHARMACEUTICALS INC
781 Chestnut Ridge Road • P. O. Box 4310 • Morgantown, West Virginia 26504-4310 U.S.A. • (304) 599-2595

NDA
NEW CORRESP
1/23/02

January 15, 2002

Office of Generic Drugs, CDER, FDA
Gary J. Buehler, Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

PATENT AMENDMENT

RE: MIRTAZAPINE TABLETS, 15MG, 30MG AND 45MG
ANDA 76-122

Dear Mr. Buehler:

This patent amendment to the Abbreviated New Drug Application (ANDA) identified above for Mirtazapine Tablets provides documentation of receipt of the notice sent to the patent and/or NDA holders with regard to the paragraph IV patent certification provided in the application. The attached correspondence from Mylan's Legal Department also provides notice that litigation against Mylan has been initiated by the patent and NDA holders with regard to the paragraph IV certification.

This amendment is submitted in duplicate. Should you have any questions regarding this amendment or require additional information, please contact the undersigned at (304) 599-2595, ext. 6600 or via facsimile at (304) 285-6407.

Sincerely,

Frank R. Sisto
Vice President
Regulatory Affairs

FRS/tlr

Enclosure

CENTER FOR DRUG EVALUATION AND RESEARCH
JAN 17 2002

Department—Fax Numbers
Accounting (304) 285-6403
Administration (304) 599-7284
Business Development (304) 599-7284
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Quality Control (304) 598-5407
Research & Development (304) 285-6409
Sales & Marketing (304) 598-3232

labeling review drafted 11/6/01 A. Vega

MYLAN PHARMACEUTICALS INC
781 Chestnut Ridge Road • P. O. Box 4310 • Morgantown, West Virginia 26504-4310 U.S.A. • (304) 599-2595

October 25, 2001

CMC AMENDMENT N/AC

Office of Generic Drugs, CDER, FDA
Gary J. Buehler, Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

MAJOR AMENDMENT
(CMC AND LABELING INFORMATION ENCLOSED)

CENTER FOR DRUG EVALUATION AND RESEARCH
OCT 26 2001
OGD

RE: MIRTAZAPINE TABLETS, 15MG, 30MG AND 45MG
ANDA 76-122
RESPONSE TO AGENCY CORRESPONDENCES DATED AUGUST 8, 2001 AND AUGUST 30, 2001

Dear Mr. Buehler:

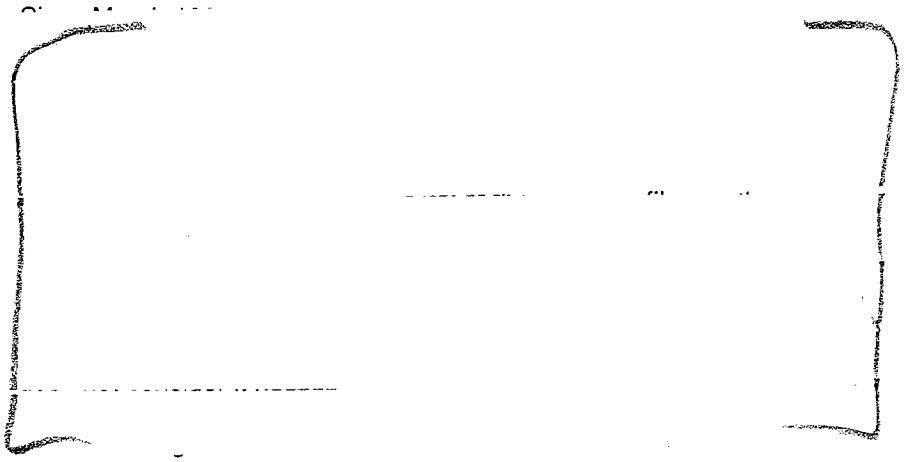
Reference is made to the Abbreviated New Drug Application (ANDA) identified above, which is currently under review, and to the Agency's August 8, 2001 correspondence pertaining to this application (provided in Attachment U). In response to the Agency's comments of August 8th, Mylan wishes to amend this application as follows.

A. DEFICIENCIES

FDA COMMENT 1: The master batch record does not clearly indicate the quantity of [redacted] Please provide more detailed instructions for this stage of the manufacturing process including the specific quantity of [redacted] necessary to [redacted] tablet batch.

MYLAN RESPONSE:

[redacted]



FDA COMMENT 2: OGD's Bioequivalence Division has recommended dissolution specifications that are tighter than those proposed in your application. We recommend that you review your release and stability specifications to comply with the Bioequivalence Division's recommendation below.

"The dissolution testing should be conducted in [redacted] *using* [redacted] *The test product should meet the following specifications as recommended by the Agency:*

Not less than [redacted] *Q) of the labeled amount of Mirtazapine in the dosage form is dissolved in 15 minutes."*

MYLAN RESPONSE: In accordance with the Bioequivalence Division's recommendation, Mylan has tightened the dissolution specification for release and stability to "Not less than [redacted] Q) of the labeled amount of Mirtazapine in the dosage form is dissolved in 15 minutes" and the medium was changed from [redacted] to [redacted] Please find revised dissolution profile data for Mylan's Mirtazapine Tablets and the Reference Listed Drug, Remeron® in Attachment E. The revised finished product specifications, Certificates of Analysis for the submitted drug product lots (R1J0334, R1J0335 and R1H3105), revised dissolution procedure, and revised pre- and post-approval stability protocols are provided in Attachments, F, G, H and I, respectively. Stability data reflecting the revised dissolution criteria is provided in Attachment J. The method validation for the revised dissolution procedure is provided in Attachment K. Also included in these attachments are revisions to documents pertaining to Mirtazapine Tablets, 15mg and 30mg. The amendment to the original ANDA submission to provide for these additional strengths was submitted on June 29, 2001.

The upper limit of the hardness ranges for core tablets have been adjusted to accommodate the tightened dissolution specification. The hardness ranges have been revised as follows:

	submitted	revised
15mg	[redacted]	[redacted]
30mg	[redacted]	[redacted]
45mg	[redacted]	[redacted]

The revised pre-compression, in-process and core specifications for Mirtazapine Tablets, 15mg, 30mg and 45mg are provided in Attachment L. Provided in Attachment M is dissolution data to support the revised in-process hardness ranges.

FDA COMMENT 3: We recommend that you tighten the Assay specifications for release of the drug product to more accurately describe the purity of the drug product.

MYLAN RESPONSE: Mylan acknowledges the Agency's request to tighten the Assay specifications for release of the drug product to more accurately describe the purity of the drug product. Accordingly, Mylan has tightened the specifications from ' [redacted] for release of the drug product. The revised finished product specifications, Certificates of Analysis for the submitted drug product lots (R1J0334, R1J0335 and R1H3105) pre- and post-approval stability protocols are provided in Attachments F, G and I, respectively. Also included in these attachments are revisions to documents pertaining to Mirtazapine Tablets, 15mg and 30mg. The amendment to the original ANDA submission to provide for these additional strengths was submitted on June 29, 2001.

FDA COMMENT 4: We recommend that you develop an [redacted] method as an assay method rather than using a potentiometric method to measure the potency of the drug substance.

MYLAN RESPONSE: In response to the Agency's comment, Mylan Pharmaceuticals has adopted an [redacted] method for the determination of assay for the drug substance. This assay method is the same as Mylan's submitted and validated stability indicating assay method for the finished product. The method was validated for Linearity and Range, Accuracy, Specificity, Repeatability and [redacted] and Standard and Sample Solution Stability. Mylan Pharmaceuticals refers the reviewer to Section XV, p. 3498 of our original ANDA application and to Section XV, p. 1086 of the amendment to the original ANDA submission that provides for additional strengths, for the applicable finished product method validations. The assay procedure, drug substance specifications and Certificate of Analysis for lot 1B032 are provided in Attachments N, O, and P, respectively.

FDA COMMENT 5: We request that you identify the degradants that appear when the drug substance is exposed to light. We refer to the table on page 3518. Please also describe the physical appearance of the sample following light exposure. We also note that the chromatograms taken following [redacted] do not support your conclusion regarding the formation of ' [redacted] We refer to pages 3529 and 3536.

MYLAN RESPONSE: Mylan acknowledges the agency's request to identify the degradants that appear when the drug substance was exposed to light, as reported in the submitted specificity report. Mylan would like to bring to the reviewer's attention that light degradants were generated by extremely harsh light exposure of the drug substance. The drug substance was exposed to not less than [redacted] of intense light for five days. Per the reviewer's request, Mylan describes the physical appearance of the drug substance following light exposure as "a white to yellowish white crystalline powder whose surface has developed a slight red/orange shading." These extreme conditions are not representative of typical exposure of the drug substance, which is clearly labeled from the manufacturer as "Highly Sensitive to Light." The purpose of the light study was to demonstrate that the method is capable of detecting light degradants if they should arise.

Mylan assures the levels of these impurities are low by controlling for all impurities (known and unknown) in the drug substance with a "not more than [redacted] individual impurity" specification and a "not more than [redacted] total impurities" specification. Mylan considers these impurity specifications to be very low and in accordance with the Guidance for Industry, "ANDAs: Impurities in Drug Substances."

In addition, light degradation is not observed in the drug product when it is exposed to the same conditions as for the drug substance (i.e. not less than [redacted] of intense light for five days) as documented in the table on page 3518 of the application. Mylan has included, for review, one-month of stability data for the drug product in the proposed container/closure systems that were exposed to the same harsh light stress conditions of not less than [redacted] of intense light for one month. This clearly demonstrates that no significant amount of degradation is attributed to harsh light stresses. Please refer to the stability and chromatograms associated with the one-month light stress stability station in Attachment Q and R, respectively.

Regarding product exposure to peroxide, the chromatograms provided on pages 3529 and 3536 of the original ANDA application that were taken following exposure to peroxide do not appear to support the conclusion regarding the formation of [redacted], since these chromatograms are representative of the Assay (i.e., the Assay chromatograms scale does not provide adequate visual representation of impurity peaks). By examining related compounds example chromatograms, it is clearly demonstrated that the impurity resulting from [redacted] stress is the [redacted] mpurity. Therefore, Mylan wishes to refer the reviewer to chromatograms for the specificity of the related compounds method provided in Attachment S which also includes PDA spectrum analysis of the peak compared with spectrum of the [redacted]. The characteristic spectrum matches the sample compared to [redacted].

In addition to responding to the deficiencies above please note and acknowledge the following:

FDA COMMENT: Drug Master File [redacted] submitted by [redacted], has been reviewed and found to be inadequate. We have requested further information from [redacted] to resolve our questions regarding the DMF. Please note that we cannot complete our review of ANDA 76-122 until the DMF is found to be adequate.

MYLAN RESPONSE: Mylan acknowledges the Agency's comment that DMF # [redacted] submitted by [redacted], was found inadequate and that further information was required. It is noted that a satisfactory resolution regarding the DMF is required to resume review of the ANDA. Enclosed in Attachment T is a copy of a cover letter from [redacted] or DMF [redacted] indicating that the update to the DMF was completed and forwarded to the FDA on [redacted] behalf on August 28, 2001.

B. REGARDING LABELING DEFICIENCIES (Agency's August 30, 2001 correspondence)

The Agency initially provided labeling comments in the August 8, 2001 correspondence. Subsequently, the Agency forwarded additional labeling comments in a correspondence dated August 30, 2001. The August 30th correspondence incorporated the Agency's labeling comments from the August 8th correspondence. Accordingly, the deficiencies addressed below are those provided in the August 30th correspondence.

FDA COMMENT 1. GENERAL COMMENT: Please note that some of the comments below are the same as those faxed to you on August 8, 2001.

MYLAN RESPONSE: Mylan acknowledges that the Agency sent two separate facsimiles regarding labeling deficiencies associated with Mirtazapine Tablets. Both pieces of correspondence are included in Attachment U for the reviewer's reference. In addition, Mylan also acknowledges that all labeling deficiencies listed in the Agency's correspondence dated August 8, 2001 are also presented in the Agency's August 30, 2001 correspondence. However, the August 30, 2001 correspondence also contains additional labeling deficiencies. Thus, for the purpose of revising the labeling, Mylan referred to the August 30, 2001 correspondence.

FDA COMMENT 2 CONTAINER: We encourage you to distinguish your product strengths by boxing, contrasting colors, or some other means.

MYLAN RESPONSE: When the bottle labeling goes to final print, the drug name/strength will be printed in a color unique to each strength. This will provide differentiation between the bottle labels for different strengths. Since there were no other deficiencies listed for Mylan's bottle labeling, Mylan is not re-submitting draft bottle labeling at this time.

FDA COMMENT 3. INSERT: (See Attachment U – Agency Correspondence Dated August 30, 2001 for details regarding the requested revisions).

MYLAN RESPONSE: Four (4) draft copies of the revised prescribing information (Code MTZP:RX2, revised October 2001) are provided in Attachment W. The enclosed prescribing information incorporates the revisions requested in the Agency's facsimile of August 30, 2001. A copy of the August 30, 2001 correspondence is provided in Attachment U for the convenience of the reviewer. Mylan will submit 12 final printed copies of all bottle labels and outsert labeling at least 60 days prior to full approval of this application.

In order to facilitate the review of this labeling, Attachment V contains a side-by-side comparison of the revised draft outsert (MTZP:RX2) to the draft outsert that was previously submitted (MTZP:RX1). It is noted that prior to approval of this application, the Agency may find factors in the labeling unacceptable and may request further changes to the labeling. In addition, Mylan may have to revise our labeling pursuant to approved changes for the reference listed drug. Mylan will monitor the FDA's website for any approved labeling changes.

Pursuant to 21 CFR 314.96(b), we certify that a true copy of the technical sections of this amendment, as submitted to the Office of Generic Drugs, has been forwarded to the FDA's Baltimore District Office.

This amendment is submitted in duplicate. Should you require additional information or have any questions regarding this amendment, please contact the undersigned at (304) 599-2595, ext. 6600 or via facsimile at (304) 285-6407.

Sincerely,

Frank R. Sisto
Vice President
Regulatory Affairs

FRS/dn

Enclosure

Please file in latest open archival volume 76-122

FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER, L.L.P.
1300 I STREET, N. W.
WASHINGTON, DC 20005-3315

202 • 408 • 4000
FACSIMILE 202 • 408 • 4400

ATLANTA
404•653•6400
PALO ALTO
650•849•6600

BASIL J. LEWRIS
202-408-4089
bill.lewris@finnegan.com

TOKYO
011•813•3431•6943
BRUSSELS
011•322•646•0353

August 17, 2001

NEW CORRESP
Patent & Legal

Food & Drug Administration
Office of Generic Drugs
(HFD-600)
7500 Standish Place
Rockville, Maryland 20855

HAND DELIVERY VIA WASHINGTON EXPRESS SERVICES, INC.

Attn: Mr. Gregory Davis

Mirtazapine Tablets, 15 mg and 30 mg
Abbreviated New Drug Application No. 76-122
Notification of Filing of Legal Action for Patent Infringement

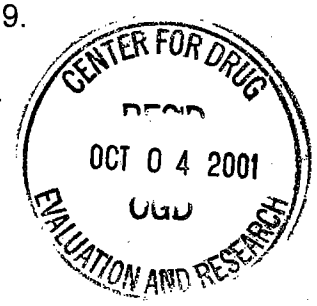
Dear Mr. Davis:

We represent Akzo Nobel N.V. (Akzo Nobel) and Organon Inc. (Organon), the owner and exclusive licensee, respectively, of United States Patent No. 5,977,099. Organon is also the owner of New Drug Application No. 20-415. We are sending you this letter on behalf of our clients pursuant to 21 C.F.R. § 314.107(f)(2) to notify you of the following:

(1) Shelly Monteleone, Associate Patent Counsel of Mylan Pharmaceuticals, Inc. (Mylan), sent a letter to Akzo Nobel and Organon dated July 5, 2001, stating that Mylan was providing information pursuant to 21 U.S.C. § 355(j)(2)(B)(ii). The letter included the following information:

(i) Mylan submitted to the FDA an abbreviated new drug application (ANDA) which contains any required bioavailability or bioequivalence data or information, and which seeks approval to engage in the commercial manufacture, use, and sale of mirtazapine tablet, oral, before the expiration date of U.S. Patent No. 5,977,099.

(ii) The ANDA number is ANDA 76-122.



(iii) The established names of the proposed drug products are "mirtazapine tablet; oral; 15 mg and mirtazapine tablet; oral; 30 mg."

(iv) The active ingredient, strength, and dosage form of the proposed drug products are mirtazapine 15 mg and 30 mg tablets for oral administration.

(v) The patent number and expiration date of the patent which Mylan alleges not to be infringed is United States Patent No. 5,977,099, which expires June 16, 2017.

(2) Organon received Mylan's letter on or about July 9, 2001.

CERTIFICATION

We hereby certify that on August 13, 2001, Akzo and Organon filed an action for patent infringement against Mylan in the United States District Court for the District of New Jersey (Civil Action No. 01-3835 (FSH)). Akzo and Organon state, among other things, that under 35 U.S.C. § 271(e)(2)(A) Mylan's submission to the FDA of an ANDA to obtain approval for the commercial manufacture, use, or sale of 15 mg and 30 mg mirtazapine tablets before the expiration of United States Patent No. 5,977,099 was an infringement of United States Patent No. 5,977,099.

We, therefore, respectfully request that the approval of Mylan's ANDA for 15 mg and 30 mg mirtazapine tablets shall not be made effective until at least the expiration of the 30-month period as provided by 21 U.S.C. § 355(j)(5)(B)(iii), subject to an appropriate ruling by the Court.

Sincerely,

FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER, L.L.P.

By _____
Basil J. Lewris

BJL:kd(rcw)

cc: Shelly Monteleone, Esq. (via first class mail)
Associate Patent Counsel
Mylan Pharmaceuticals Inc.
781 Chestnut Ridge Road
P. O. Box 4310
Morgantown, West Virginia 26504

MYLAN PHARMACEUTICALS INC
781 Chestnut Ridge Road • P. O. Box 4310 • Morgantown, West Virginia 26504-4310 U.S.A. • (304) 599-2595

BIOAVAILABILITY

7/25/01 Add 2 new strengths to 5 Middleton

June 29, 2001

labeling review drafted 8/30/01 A. Vezza

Concur. 27-JUL-2001 Gregory S. Carr

MAJOR AMENDMENT
CMC AND BIOWAIVER INFORMATION ENCLOSED

Office of Generic Drugs, CDER, FDA
Gary J. Buehler, Acting Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ORIG AMENDMENT
Ac

RE: MIRTAZAPINE TABLETS, 45MG
ANDA 76-122
(Amendment to Provide for Addition of 15mg and 30mg Strengths)

Dear Mr. Buehler:

Mylan wishes to amend the above referenced application to provide for the manufacture of Mirtazapine Tablets, 15mg and 30mg, as product line extensions to Mylan's ANDA for Mirtazapine Tablets, 45mg (ANDA 76-122) submitted on February 27, 2001.

The proposed strengths are qualitatively identical and compositionally proportional to the 45mg strength, and will be manufactured, tested, packaged, and labeled using procedures and controls similar to those provided in Mylan's ANDA 76-122 submitted on February 27, 2001. The bioequivalence of Mylan's Mirtazapine Tablets, 45mg and the reference listed drug, Remeron® Tablets 45mg, was demonstrated in Mylan's original submission, ANDA 76-122. Based on the compositional proportionality of the 15mg, 30mg and 45mg strengths and the bioequivalence of the 45mg product, Mylan is requesting a waiver of *in vivo* bioequivalence testing requirements for the additional strengths.

CENTER FOR DRUG EVALUATION AND RESEARCH
JUL 0 2 2001
OGD

This amendment consists of 9 volumes as follows:
- Archival Copy - 3 volumes.
- Review Copy - 4 volumes.
  - Technical Section For Chemistry - 3 volumes.
  - Technical Section For Pharmacokinetics - 1 volume.
- Analytical Methods - 2 extra copies; 1 volume each.

As an aid to the reviewer, this amendment has been assembled according to the traditional ANDA format. Only those documents that have been revised since the original submission and new documents in support of the additional strengths are provided in this submission. Details of revisions made to previously submitted documents are provided on the cover page to the appropriate section of this amendment containing the revised documents. The enclosed Table of Contents provides a listing of the information being submitted in support of this amendment.

We certify that a true copy of the technical sections of this amendment, as submitted to the Office of Generic Drugs, has been forwarded to the FDA's Baltimore District Office.

Department—Fax Numbers		Information Systems	(304) 285-6404	Purchasing	(304) 598-5401
Accounting	(304) 285-6403	Label Control	(800) 848-0463	Quality Control	(304) 598-5407
Administration	(304) 599-7284	Legal Services	(304) 598-5408	Research & Development	(304) 285-6409
Business Development	(304) 599-7284	Maintenance & Engineering	(304) 598-5411	Sales & Marketing	(304) 598-3232
Human Resources	(304) 598-5406	Medical Unit	(304) 598-5445		

All correspondence regarding this application should be directed to the attention of the undersigned at Mylan Pharmaceuticals Inc., P.O. Box 4310, 781 Chestnut Ridge Road, Morgantown WV, 26504-4310. Telephone and facsimile inquiries may also be directed to the undersigned at telephone number (304) 599-2595, extension 6600 and/or facsimile number (304) 285-6407.

Sincerely,

Vincent Mancinelli II for

Frank R. Sisto
Vice President
Regulatory Affairs

FRS/dn

APPEARS THIS WAY
ON ORIGINAL

MYLAN PHARMACEUTICALS INC
781 Chestnut Ridge Road • P. O. Box 4310 • Morgantown, West Virginia 26504-4310 U.S.A. • (304) 599-2595

June 29, 2001

Office of Generic Drugs, CDER, FDA
Gary J. Buehler, Acting Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

NC

GRATUITOUS BIOEQUIVALENCE AMENDMENT
(Bioequivalence and Electronic Data Enclosed)

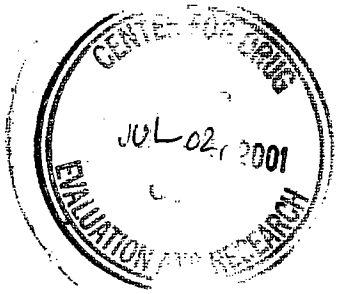
RE: ANDA 76-122; MIRTAZAPINE TABLETS, 45MG

Dear Mr. Buehler:

Reference is made to the Abbreviated New Drug Application (ANDA) identified above, which is currently under review. The original ANDA, submitted on February 27, 2001, provided fasting (MIRT-0020) and post-prandial (MIRT-0021) bioequivalence studies that demonstrated the bioequivalence of Mylan's 45 mg mirtazapine to Organon's Remeron® 45 mg tablets. Mylan measured both the parent compound, mirtazapine and its metabolite, desmethylmirtazapine during the bioanalytical testing of the samples from these studies. The concentrations for both compounds were presented in the study reports. An interfering peak was observed in the desmethylmirtazapine bioanalytical evaluation. Since the Agency's Guidance entitled "Bioavailability and Bioequivalence Studies for Orally Administered Drug Products – General Considerations" issued October 2000 (pages 18 and 19) does not require that the metabolite, desmethylmirtazapine be measured, bioequivalence was based only on the parent drug.

Although Mylan still contends that the metabolite, desmethylmirtazapine, does not need to be measured pursuant to the October 2000 Guidance, Mylan modified and revalidated the assay method. The revalidated method eliminates the interfering peak in the desmethylmirtazapine bioanalytical evaluation. The revalidated method was used to reassy all samples from the fasting (MIRT-0020) and post-prandial (MIRT-0021) studies for mirtazapine and its metabolite, desmethylmirtazapine. Both the parent drug and metabolite were analyzed with a confidence interval approach. The data obtained from the reanalysis support the conclusion from the original analysis that Mylan's 45 mg mirtazapine tablets are bioequivalent to Organon's Remeron® 45 mg tablets. The pharmacokinetic and statistical analyses performed on the reassayed values and the results are presented in the attached reports that are provided as an addendum to the original bioequivalence study reports. Although the data from the initial analysis should be considered adequate to support the bioequivalence of the referenced product, Mylan is submitting the data from this new analysis for informational purposes.

This amendment is submitted in duplicate. Should you require additional information or have any questions regarding this amendment, please contact the undersigned at (304) 599-2595, ext. 6600 or via facsimile at (304) 285-6407.



Sincerely,

Frank R. Sisto
Vice President, Regulatory Affairs

Enclosures

Department—Fax Numbers		Information Systems	(304) 285-6404	Purchasing	(304) 598-5401
Accounting	(304) 285-6403	Label Control	(800) 848-0463	Quality Control	(304) 598-5407
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Human Resources	(304) 598-5406	Medical Unit	(304) 598-5445		

MYLAN PHARMACEUTICALS INC
781 Chestnut Ridge Road • P. O. Box 4310 • Morgantown, West Virginia 26504-4310 U.S.A. • (304) 599-2595

June 13, 2001

N/AB
ORIG AMENDMENT

Office of Generic Drugs, CDER, FDA
Gary J. Buehler, Acting Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

BIOEQUIVALENCY AMENDMENT
(CMC INFORMATION ENCLOSED)

RE: MIRTAZAPINE TABLETS, 45MG
ANDA 76-122
RESPONSE TO AGENCY CORRESPONDENCE DATED MAY 30, 2001

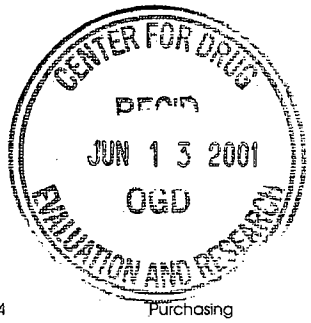
Dear Mr. Buehler:

Reference is made to the Abbreviated New Drug Application (ANDA) identified above and to the Agency's comments which were provided to Mylan in a correspondence dated May 30, 2001 (provided in Attachment J). In response to the Agency's comments of May 30th, Mylan wishes to amend this application as follows.

FDA COMMENT 1: Please explain in detail the reason for the missing 8 blood samples in the fasting study and 22 blood samples from the non-fasting study. These blood samples were not received by the analytical facility. See volume 1.2, p. 461 (MIRT-00210) and volume 1.5, p. 1816 (MIRT-0021).

MYLAN RESPONSE: According to our records, 10 samples were not provided by the clinical site for the fasting study (MIRT-0020). These samples are outlined in Table T2, Blood Collection Deviations, Mylan #MIRT-0020; CPR-MI, volume 4, p. 1109 of the original submission (see Attachment A). Of the 10 samples, 2 samples (subject 21, phase I, hours 72 and 96) were from a volunteer that did not complete the biostudy. The other 8 samples were not collected due to the volunteer being absent at the sample collection time.

According to our records only 21 samples were not provided by the clinical site for the non-fasting study (MIRT-0021). These samples are outlined in Table T2, Blood Collection Deviations, Mylan #MIRT-0021; CPR-MI2, volume 1.6, p. 2359 of the original submission (see Attachment B). The 21 samples were not collected due to the volunteer being absent at the sample collection time.



Department—Fax Numbers		Information Systems	(304) 285-6404	Purchasing	(304) 598-5401
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Human Resources	(304) 598-5406	Medical Unit	(304) 598-5445		

FDA COMMENT 2: Please repeat dissolution testing for both test and reference products using the same batches that are used in the bioequivalence studies, applying the following testing conditions with 12 individual units:

Apparatus: [redacted]
Paddle Speed: [redacted]
Medium: [redacted]
Sampling times: 5, 10, 15, 20 and 30 minutes

Please note that the requested medium is 0.1 N HCl.

MYLAN RESPONSE: Mylan acknowledges the Agency's request to repeat the dissolution testing for both the test and reference products using the same batches that were used in the bioequivalence studies. The dissolution profiles with the requested testing conditions are provided in Attachment C.

FDA COMMENT 3: Please submit data to support the long-term stability of mirtazapine in frozen study samples for the period equal to the time from the first sample collection to the day the last sample was analyzed (99 days).

MYLAN RESPONSE: A long-term frozen stability profile (including days 0, 95 and 166) of Mirtazapine and Desmethylmirtazapine was conducted in Mylan's Bioanalytical Laboratory. Mirtazapine and Desmethylmirtazapine were found to be stable in human plasma for at least 166 days while stored at a nominal temperature of -70°C, exceeding the 99 days required for MIRT-0020 and MIRT-0021 studies. The supporting data is provided in Attachment D.

FDA COMMENT 4: Please provide the detailed SOP's for the methodology (including SOP L-301). The SOP's should include the acceptance criteria for QC samples and repeat analysis.

MYLAN RESPONSE: As requested, Mylan has provided the detailed SOP's for the analytical methodology (including Bioanalytical Methods Validation SOP L-301-01) and the SOP's which include the acceptance criteria for QC samples and repeat analysis. The appropriate documents are provided as the following attachments:

Attachment E:	Analytical Methodology (Project Number 00-014-03) Upon preparing these responses, it was discovered that a typographical error was made in the Introduction section of the MIRT-0020 and MIRT-0021 analytical reports. The project number referenced was 00-014-02, it should have been 00-014-03.	
Attachment F:	L-301-01	Bioanalytical Methods Validation
Attachment G:	D-401-01	Evaluation and Acceptance Criteria for Standard Curves, Quality Controls and Biostudy Sample Batches
Attachment H:	D-400-01	Reassay or Reinjection of Clinical Samples
Attachment I:	D-416-00	Reassay of Whole Subjects

Pursuant to 21 CFR 314.96(b), we certify that a true copy of the technical sections of this amendment, as submitted to the Office of Generic Drugs, has been forwarded to the FDA's Baltimore District Office.

This amendment is submitted in duplicate. Should you require additional information or have any questions regarding this amendment, please contact the undersigned at (304) 599-2595, ext. 6600 or via facsimile at (304) 285-6407.

Sincerely,

Vincent Mancinelli II for

Frank R. Sisto
Vice President
Regulatory Affairs

FRS/dn

Enclosure

APPEARS THIS WAY
ON ORIGINAL

Please file in latest open archival volume

76-122

FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER, L.L.P.
1300 I STREET, N. W.
WASHINGTON, DC 20005-3315

202 • 408 • 4000
FACSIMILE 202 • 408 • 4400

ATLANTA
404•653•6400
PALO ALTO
650•849•6600

BASIL J. LEWRIS
202-408-4089

NEW CORRESP

DC

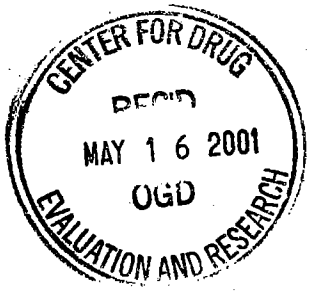
TOKYO
011•813•3431•6943
BRUSSELS
011•322•646•0353

May 7, 2001

Shelly Monteleone
NTI
5/22/01

Food & Drug Administration
Office of Generic Drugs
(HFD-600)
7500 Standish Place
Rockville, MD 20855

Attn: Mr. Gregory Davis



HAND DELIVERY VIA WASHINGTON EXPRESS SERVICES, INC.

Mirtazapine Tablets, 45mg
Abbreviated New Drug Application No. 76-122
Notification of Filing of Legal Action for Patent Infringement

Dear Mr. Davis:

We represent Akzo Nobel N.V. (Akzo Nobel) and Organon Inc. (Organon), the owner and exclusive licensee, respectively, of United States Patent No. 5,977,099. Organon is also the owner of New Drug Application No. 20-415. We are sending you this letter on behalf of our clients pursuant to 21 C.F.R. § 314.107(f)(2) to notify you of the following:

(1) Shelly Monteleone, Assistant Patent Counsel of Mylan Pharmaceuticals, Inc. (Mylan), sent a letter to Akzo Nobel and Organon dated March 22, 2001, stating that Mylan was providing information pursuant to 21 U.S.C. § 355(j)(2)(B)(ii). The letter included the following information:

(i) Mylan submitted to the FDA an abbreviated new drug application (ANDA) which contains any required bioavailability or bioequivalence data or information, and which seeks approval to engage in the commercial manufacture, use, and sale of mirtazapine tablet, oral, before the expiration date of U.S. Patent No. 5,977,099.

(ii) The ANDA number is ANDA 76-122.

(iii) The established name of the proposed drug product is "mirtazapine tablet; oral; 45mg."

(iv) The active ingredient, strength, and dosage form of the proposed drug product is mirtazapine 45mg tablets for oral administration.

(v) The patent number and expiration date of the patent which Mylan alleges not to be infringed is United States Patent No. 5,977,099, which expires June 16, 2017.

(2) Organon received Mylan's letter on or about March 26, 2001.

CERTIFICATION

We hereby certify that on May 4, 2001, Akzo and Organon filed an action for patent infringement against Mylan in the United States District Court for the District of New Jersey. The undersigned will supplement this letter with an identification of the civil action number of the District Court action as soon as this information is received. Akzo and Organon state, among other things, that under 35 U.S.C. § 271(e)(2)(A) Mylan's submission to the FDA of an ANDA to obtain approval for the commercial manufacture, use, or sale of 45mg mirtazapine tablets before the expiration of United States Patent No. 5,977,099 was an infringement of United States Patent No. 5,977,099.

We therefore respectfully request that the approval of Mylan's ANDA for 45mg mirtazapine tablets shall not be made effective until at least the expiration of the 30-month period as provided by 21 U.S.C. § 355(j)(4)(B)(iii), subject to an appropriate ruling by the Court.

Sincerely,

FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER, L.L.P.

By: _____
Basil J. Lewris

BJL:kd

cc: Shelly Monteleone, Esq. (via first class mail)
Assistant Patent Counsel
Mylan Pharmaceuticals Inc.
781 Chestnut Ridge Road
P. O. Box 4310
Morgantown, West Virginia 26504

MYLAN PHARMACEUTICALS INC
781 Chestnut Ridge Road • P. O. Box 4310 • Morgantown, West Virginia 26504-4310 U.S.A. • (304) 599-2595

March 30, 2001

Office of Generic Drugs, CDER, FDA
Gary J. Buehler, Acting Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

NEW CORRESP
NC

RE: ANDA 76-122; Mirtazapine Tablets, 45 mg

BIOEQUIVALENCE ELECTRONIC SUBMISSION ESD

Dear Mr. Buehler:

Reference is made to the Abbreviated New Drug Application (ANDA) for the referenced product that was submitted to the Agency on February 27, 2001. Please find enclosed a diskette providing the electronic submission, ESD, for the bioequivalence studies (fasting study MIRT-0020 and post-prandial study MIRT-0021) that were submitted in the ANDA. A copy of Mylan's declaration that the data contained on the electronic bioequivalence diskette is identical to the paper submission except as noted in the companion document is presented in Attachment 1.

Should you have any questions or require additional information, please contact the undersigned at telephone number (304) 599-2595, extension 6600 and/or facsimile number (304) 285-6407.

Sincerely,

Frank R. Sisto
Vice President
Regulatory Affairs

CENTER FOR DRUG EVALUATION AND RESEARCH
APR 02 2001

Enclosures

Department—Fax Numbers
Accounting (304) 285-6403
Administration (304) 599-7284
Business Development (304) 599-7284
Human Resources (304) 599-5406
Information Systems (304) 285-6404
Label Control (800) 848-0463
Legal Services (304) 598-5408
Maintenance & Engineering (304) 598-5411
Medical Unit (304) 598-5445
Purchasing (304) 598-5401
Quality Control (304) 598-5407
Research & Development (304) 285-6409
Sales & Marketing (304) 598-3232

Please file in latest open archival volume
76-122

FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER, L.L.P.
1300 I STREET, N. W.
WASHINGTON, DC 20005-3315

202 • 408 • 4000
FACSIMILE 202 • 408 • 4400

ATLANTA
404•653•6400
PALO ALTO
650•849•6600

BASIL J. LEWRIS
202-408-4089

TOKYO
011•813•3431•6943
BRUSSELS
011•322•646•0353

May 9, 2001

Emily Thomas
NAI
5/17/01

Food & Drug Administration
Office of Generic Drugs
(HFD-600)
7500 Standish Place
Rockville, MD 20855

VIA FEDERAL EXPRESS

Attn: Mr. Gregory Davis

NEW CORRESP

Mirtazapine Tablets, 45mg
Abbreviated New Drug Application No. 76-122
Notification of Filing of Legal Action for Patent Infringement

Dear Mr. Davis:

Following up on our letter to you of May 7, 2001, a copy of which is attached, we have now obtained the civil action number of the patent infringement action that Akzo and Organon filed against Mylan in the District Court for the District of New Jersey on May 4, 2001. The Civil Action No. is 01-2171(FSH).

Thank you for your attention to this matter.

Sincerely,

FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER, L.L.P.

By: _____
Basil J. Lewris

BJL:kd

MYLAN PHARMACEUTICALS INC
781 Chestnut Ridge Road • P. O. Box 4310 • Morgantown, West Virginia 26504-4310 U.S.A. • (304) 599-2595

March 22, 2001

NC

NEW CORRESP

Office of Generic Drugs, CDER, FDA
Gary J. Buehler, Acting Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

PATENT AMENDMENT

Emily Thomas NTL 3/29/01

RE: MIRTAZAPINE TABLETS, 45MG
ANDA 76-122

Dear Mr. Buehler:

Enclosed is an amended patent certification pertaining to the above referenced ANDA, which was submitted to the Agency on February 27, 2001. This amended certification addresses U.S. Patent Number 5,178,878 which was recently added to the Patent Term Extension and New Patents Information listed on FDA's website (March 19, 2001, Docket Number 95S-0177).

This patent amendment is submitted in duplicate. Should you have any questions or require additional information, please contact the undersigned by telephone at (304) 599-2595, ext. 6600 or by facsimile at (304) 285-6407.

Sincerely,

Frank R. Sisto
Vice President
Regulatory Affairs

FRS/tlr

Enclosure

CENTER FOR DRUG EVALUATION AND RESEARCH
RECD
MAR 23 2001
OGD

cc: Bonnie McNeal (via facsimile)

Department—Fax Numbers		Information Systems	(304) 285-6404	Purchasing	(304) 598-5401
Accounting	(304) 285-6403	Label Control	(800) 848-0463	Quality Control	(304) 598-5407
Administration	(304) 599-7284	Legal Services	(304) 598-5408	Research & Development	(304) 285-6409
Business Development	(304) 599-7284	Maintenance & Engineering	(304) 598-5411	Sales & Marketing	(304) 598-3232
Human Resources	(304) 598-5406	Medical Unit	(304) 598-5445		

ANDA 76-122

Mylan Pharmaceuticals Inc.
Attention: Frank Sisto
781 Chestnut Ridge Road
Morgantown, WV 26504

MAR 14 2001

Dear Sir:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

NAME OF DRUG: Mirtazapine Tablets, 45 mg

DATE OF APPLICATION: February 27, 2001

DATE (RECEIVED) ACCEPTABLE FOR FILING: February 28, 2001

You have filed a Paragraph IV patent certification, in accordance with 21 CFR 314.94(a)(12)(i)(A)(4) and Section 505(j)(2)(A)(vii)(IV) of the Act. Please be aware that you need to comply with the notice requirements, as outlined below. In order to facilitate review of this application, we suggest that you follow the outlined procedures below:

CONTENTS OF THE NOTICE

You must cite section 505(j)(2)(B)(ii) of the Act in the notice and should include, but not be limited to, the information as described in 21 CFR 314.95(c).

SENDING THE NOTICE

In accordance with 21 CFR 314.95(a):

- Send notice by U.S. registered or certified mail with return receipt requested to each of the following:

  1) Each owner of the patent or the representative designated by the owner to receive the notice;

2) The holder of the approved application under section 505(b) of the Act for the listed drug claimed by the patent and for which the applicant is seeking approval.

3) An applicant may rely on another form of documentation only if FDA has agreed to such documentation in advance.

DOCUMENTATION OF NOTIFICATION/RECEIPT OF NOTICE

You must submit an amendment to this application with the following:

- In accordance with 21 CFR 314.95(b), provide a statement certifying that the notice has been provided to each person identified under 314.95(a) and that notice met the content requirements under 314.95(c).

- In accordance with 21 CFR 314.95(e), provide documentation of receipt of notice by providing a copy of the return receipt or a letter acknowledging receipt by each person provided the notice.

- A designation on the exterior of the envelope and above the body of the cover letter should clearly state "PATENT AMENDMENT". This amendment should be submitted to your application as soon as documentation of receipt by the patent owner and patent holder is received.

DOCUMENTATION OF LITIGATION/SETTLEMENT OUTCOME

You are requested to submit an amendment to this application that is plainly marked on the cover sheet "PATENT AMENDMENT" with the following:

- If litigation occurs within the 45-day period as provided for in section 505(j)(4)(B)(iii) of the Act, we ask that you provide a copy of the pertinent notification.

- Although 21 CFR 314.95(f) states that the FDA will presume the notice to be complete and sufficient, we ask that if you are not sued within the 45-day period, that you provide a letter immediately after the 45 day period elapses, stating that no legal action was taken by each person provided notice.

- You must submit a copy of a court order or judgement or a settlement agreement between the parties, whichever is applicable, or a licensing agreement between you and the patent holder, or any other relevant information. We ask that this information be submitted promptly to the application.

If you have further questions you may contact Gregg Davis, Chief, Regulatory Support Branch, at (301) 827-5862.

We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

Bonnie McNeal
Project Manager
(301) 827-5849

Sincerely yours,

Gregory S. Davis for

Wm Peter Rickman
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

MYLAN PHARMACEUTICALS INC
781 Chestnut Ridge Road • P. O. Box 4310 • Morgantown, West Virginia 26504-4310 U.S.A. • (304) 599-2595

labeling review
drafted 4/3/01
A. Vezza

February 27, 2001

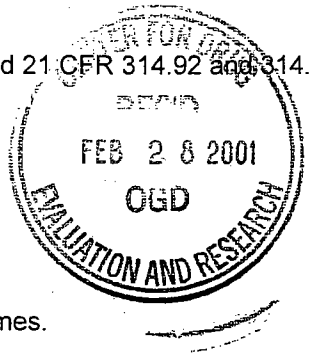
ELECTRONIC DATA ENCLOSED
BIOEQUIVALENCE DATA ENCLOSED

505(j)(2)(A) OK
14-MAR-2001
Gregory S. Davis

Office of Generic Drugs, CDER, FDA
Gary J. Buehler, Acting Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: MIRTAZAPINE TABLETS, 45MG

Dear Mr. Buehler:



Pursuant to section 505(j) of the Federal Food, Drug and Cosmetic Act and 21 CFR 314.92 and 314.94, we submit the enclosed abbreviated new drug application for:

Proprietary Name: None
Established Name: Mirtazapine Tablets
This application consists of a total of 19 volumes.
Archival Copy - 8 volumes.
Review Copy - 9 volumes.
Technical Section For Chemistry - 3 volumes.
Technical Section For Pharmacokinetics - 6 volumes.
Analytical Methods - 2 extra copies; 1 volume each.
NOTE: The Technical Section for Pharmacokinetics of the review copy and the archival copy each contain a set of data diskettes for the bioequivalence studies conducted in support of this application. In addition, the diskettes providing the Bioequivalence Electronic Submission ESD (BA/BE) EVA will be forwarded to the Agency within the 30 day grace period.

This application provides for the manufacture of Mirtazapine Tablets, 45mg. Mylan Pharmaceuticals Inc., 781 Chestnut Ridge Road, Morgantown, WV 26505-2730, performs all operations in the manufacture, packaging, and labeling of the drug product.

It should be noted that this Abbreviated New Drug Application has been organized according to the Agency's February 1999 Guidance for Industry - 'Organization of an ANDA'. Pursuant to this guidance, Mylan commits to resolve any issues identified in the methods validation process after approval.

Department—Fax Numbers		Information Systems	(304) 285-6404	Purchasing	(304) 598-5401
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Human Resources	(304) 598-5406	Medical Unit	(304) 598-5445		

As required by 21 CFR 314.94(d)(5), we certify that a true copy of the technical sections of this application, as submitted to the Office of Generic Drugs, has been forwarded to the FDA's Baltimore District Office. The following Table of Contents and Reader's Guide detail the documentation submitted in support of this application.

All correspondence regarding this application should be directed to the attention of the undersigned at Mylan Pharmaceuticals Inc., P.O. Box 4310, 781 Chestnut Ridge Road, Morgantown WV, 26504-4310. Telephone and facsimile inquiries may also be directed to the undersigned at telephone number (304) 599-2595, extension 6600 and/or facsimile number (304) 285-6407.

Sincerely,

Vincent Mancinelli II for

Frank R. Sisto
Vice President
Regulatory Affairs

FRS/dn