

CENTER FOR DRUG EVALUATION AND RESEARCH

**APPLICATION NUMBER:
76-119**

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Approval Package for:

APPLICATION NUMBER:

76-119

Generic Name: Mirtazapine Tablets
15mg, 30mg, and 45mg

Sponsor: TEVA Pharmaceuticals USA

Approval Date: January 24, 2003

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RESEARCH**

APPLICATION NUMBER:

76-119

APPROVAL LETTER

ANDA 76-119

JAN 24 2003

TEVA Pharmaceuticals USA
Attention: Philip Erickson
1090 Horsham Road
P.O. Box 1090
North Wales, PA 19454-1090

Dear Sir:

This is in reference to your abbreviated new drug application (ANDA) dated February 26, 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 made to our Tentative Approval letters dated January 15, 2002, and October 8, 2002, and to your amendments dated November 25, 2002; and January 7, and January 22, 2003. Reference is also made to your correspondence dated December 19, 2002 regarding the outcome of the patent litigation referenced below.

The listed drug referenced in your application (RLD), Remeron® Tablets of Organon Inc., is 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 No. 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. This certification states that the '099 patent is invalid, unenforceable, or will not be infringed by your manufacture, use, or sale of Mirtazapine Tablets, 15 mg, 30 mg, and 45 mg. Section 505(j)(5)(B)(iii) of the Act provides that approval of an abbreviated new drug application shall be made effective immediately, unless an action is brought against TEVA Pharmaceuticals USA (TEVA) for infringement of the '099 patent. The infringement action must be taken prior to the expiration of forty-five (45) days from the date the notice TEVA provided to the NDA/patent holder(s) under paragraph (2)(B)(i) was received. You have previously notified the agency that TEVA complied with the requirements of Section 505(j)(2)(B) of the Act, and that litigation involving your challenge to the '099 patent was initiated in the United States District Court for the District of New Jersey (Akzo Nobel N.V. and Organon Inc. v. TEVA Pharmaceuticals USA, Civil Action Number 01-2682 [FSH]).

Your communication dated December 19, 2002, provides notification to the agency that in a court order dated December 18, 2002, the district court granted the defendant's motion for summary judgement ruling that TEVA did not infringe upon the '099 patent. In response to this decision, your amendments dated December 19, 2002 and January 7, 2003, request that

the agency grant final approval for your application providing for all three tablet strengths of the drug product, i.e., 15 mg, 30 mg, and 45 mg, and that TEVA be regarded as being eligible for 180-day generic drug exclusivity for all three strengths.

As noted below, the agency concurs that TEVA is eligible for 180-day generic drug exclusivity, but only with respect to the 15 mg and 30 mg strengths of the drug product. However, the agency is continuing to resolve the issues concerning eligibility for 180-day exclusivity for the 45 mg strength. We refer to the Citizen Petition submitted to the agency on May 31, 2002 by Mylan Pharmaceuticals, Inc. on this topic. The agency's decision with regard to eligibility for 180-day generic drug exclusivity with respect to the 45 mg strength of Mirtazapine Tablets is expected in the near future. Should the agency decide that TEVA is eligible for exclusivity for the 45 mg strength, the office will issue a separate approval letter for that strength. Because the agency does not wish to delay approval of the 15 mg and

30 mg strengths of the drug product, we will continue to regard your Mirtazapine Tablets, 45 mg, as tentatively approved.

We have completed the review of this abbreviated application as amended and have concluded that based upon the information you have presented to date, your Mirtazapine Tablets 15 mg and 30 mg are safe and effective for use as recommended in the submitted labeling. The Division of Bioequivalence has determined your Mirtazapine Tablets 15 mg and 30 mg, to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Remeron® Tablets 15 mg and 30 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.

With regard to 180-day generic drug exclusivity for Mirtazapine Tablets, we have concluded that TEVA was the first applicant to submit a substantially complete ANDA containing a paragraph IV certification to the '099 patent. Therefore, with this approval, TEVA is eligible for 180-days of market exclusivity for the 15 mg and 30 mg strengths of this drug product as provided for under Section 505(j)(5)(B)(iv) of the Act. This exclusivity began to run on the date the New Jersey District Court's decision was entered in the docket, December 18, 2002.

Under section 505(A) of the Act, certain changes in the conditions described in this ANDA for the 15 mg and 30 mg strengths require an approved supplemental application before the change can be made.

Post-marketing requirements for this ANDA for the 15 mg and 30 mg strengths are set forth in 21 CFR 314.80-81. The Office of Generic Drugs should be advised of any change in the marketing status of the 15 mg and 30 mg strengths.

We request that you submit, in duplicate, any proposed advertising or promotional copy that you intend to use in your initial advertising or promotional campaign for the 15 and 30 mg strengths of this drug product. 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

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printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-240). Please do not use Form FD-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-240) with a completed Form FD-2253 at the time of their initial use.

As previously noted, should the agency conclude that TEVA is also eligible for 180-day generic drug exclusivity for Mirtazapine Tablets 45 mg, the office will issue a separate approval letter to TEVA for the 45 mg strength. In the event that another applicant is found to be eligible for the exclusivity, in order to provide for the final approval of your Mirtazapine Tablets, 45 mg, please submit a supplemental application providing the information requested beginning with the last paragraph on page 2 through page 3 of the tentative approval letter dated October 8, 2002. This information should be clearly designated in your cover letter as a "SUPPLEMENTAL APPLICATION – EXPEDITED REVIEW REQUESTED".

If you have questions about the status of this application, and prior to your submission of the supplemental application referenced above, please contact Mark Anderson, R.Ph., Project Manager, at (301) 827-5789 for further instructions.

Sincerely yours,

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

1/24/03

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APPLICATION NUMBER:

76-119

**TENTATIVE APPROVAL
LETTER(S)**

ANDA 76-119

OCT -8 2002

TEVA Pharmaceuticals USA
Attention: Phillip Erickson
1090 Horsham Road
P.O. Box 1090
North Wales, PA 19454-1090

Dear Sir:

This is in reference to your abbreviated new drug application (ANDA) dated February 26, 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 April 5, April 23, May 1, May 20, and July 5, 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 remains 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, or sale 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 TEVA Pharmaceuticals USA (TEVA) for infringement of the patent that is the subject of the certification (the '099 patent). You have notified the agency that TEVA 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. TEVA Pharmaceuticals USA, Civil Action No. 01-2682 [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,

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Gary Buehler 10/4/02
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 76-119

JAN 15 2002

TEVA Pharmaceuticals USA
Attention: Phillip Erickson
1090 Horsham Road
P.O. Box 1090
North Wales, PA 19454-1090

Dear Sir:

This is in reference to your abbreviated new drug application (ANDA) dated February 26, 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 April 12, May 2, May 11, May 14, July 27, September 10, November 27, and December 28, 2001.

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

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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.

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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.

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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,

Handwritten signature of Gary Buehler, appearing as 'G Buehler' in a stylized, cursive script.

Gary Buehler
Director

1/15/02

Office of Generic Drugs
Center for Drug Evaluation and Research

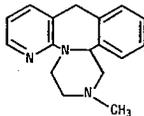
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APPLICATION NUMBER:

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FINAL PRINTED LABELING(S)

Mirtazapine tablets are an orally administered, tetracyclic chemical structure and belongs to the piperazine-azepine group of compounds. It is designated 1,2,3,4,10,14b-hexahydro-2-methylpiperazine[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 tablets containing 15 or 30 mg of mirtazapine. Each tablet also contains the following inactive ingredients: colloidal silicon dioxide, corn starch, hydroxypropyl methylcellulose, lactose monohydrate, magnesium stearate, polyethylene glycol 400, povidone, and titanium dioxide. The 15 mg-tablet also contains iron oxide yellow and polyethylene glycol 6000. The 30 mg-tablet also contains iron oxide red, iron oxide yellow, and polyethylene glycol 6000.

CLINICAL PHARMACOLOGY

Pharmacodynamics
The mechanism of action of mirtazapine tablets, 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-HT₂ and 5-HT₁ receptors. Mirtazapine has no significant affinity for the 5-HT_{1A} and 5-HT_{1B} receptors.

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

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

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

Pharmacokinetics

Mirtazapine is rapidly and completely absorbed following oral administration and has 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 plasma in very low levels. The (-) enantiomer has an elimination half-life that is approximately two to three times 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 directly 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 (Cl_{cr} = 11 to 39 mL/min/1.73 m²) and approximately 50% in patients with severe (Cl_{cr} < 10 mL/min/1.73 m²) 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 treated with mirtazapine from a dose range of 5 mg up to 35 mg/day. Overall, these studies demonstrated mirtazapine to be superior to placebo on at least three of the following four measures: 21-Item Hamilton Depression Rating Scale (HDRS) total score; HDRS Depressed Mood Item; CGI Severity score; and Montgomery and Åsberg 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

varied from 21 to 32 mg/day. A third 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 subgroups.

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 Sjoren's Syndrome) out of 2,796 patients treated with mirtazapine tablets developed agranulocytosis (absolute neutrophil count (ANC) < 500/mm³ with associated signs and symptoms, e.g., fever, infection, etc.) and a third patient developed severe neutropenia (ANC < 500/mm³ without any associated symptoms). For these three patients, onset of severe neutropenia was detected on days 61, 9, and 14 of treatment, respectively. All three patients recovered after 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, it is recommended that mirtazapine not be used in combination with a MAOI, or within 14 days of initiating or discontinuing therapy with a MAOI.

PRECAUTIONS

General

Somnolence

In U.S. controlled studies, somnolence was reported in 54% of patients treated with mirtazapine, 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 $\geq 7\%$ of body weight was reported in 7.5% of patients treated with mirtazapine, compared to 0% for placebo and 5.9% for amitriptyline. In a pool of premarketing U.S. studies, including many patients for long-term, open label treatment, 8% of patients receiving mirtazapine discontinued for weight gain. In an 8-week long pediatric clinical trial of doses between 15 to 45 mg/day, 49% of mirtazapine-treated patients had a weight gain of at least 4%, compared to 5.7% of placebo-treated patients (see PRECAUTIONS, Pediatric Use).

Cholesterol/Triglycerides

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

Transaminase Elevations

Clinically significant ALT (SGPT) elevations (> 3 times the upper limit of the normal range) were observed in 2.0% (8/424) of patients exposed to mirtazapine in a pool of short-term U.S. controlled trials, compared to 0.3% (1/328) placebo patients and 2.0% (3/161) 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 m²) and severe (GFR < 10 mL/min/1.73 m²) 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 judgment, 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, patient 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 mechanism: (e.g., pharmacodynamic, pharmacokinetic inhibition or enhancement, etc.) is: 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 substrate 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 risk 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, patient 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/m² basis in mice and rats, respectively. There was an increased incidence of hepatocellular adenoma and carcinoma in male mice at the high dose. In rats, there was an increase in hepatocellular adenoma in females at the mid and high doses and in hepatocellular tumors and thyroid follicular adenoma/cystadenoma and carcinoma in males at the high dose. The data suggest that the above effects could possibly be mediated by non-genotoxic mechanisms, the relevance of which to humans is not known.

The doses used in the mouse study may not have been high enough to fully characterize the carcinogenic potential of 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 rat 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/m² basis. Mating and conception were not affected by the drug, but estrous cycling was disrupted at doses that were 3 or more times the MRHD and pre-implantation losses occurred at 20 times the MRHD.

Pregnancy

Teratogenic Effects - Pregnancy Category C

Reproduction studies in pregnant rats and rabbits at doses up to 100 mg/kg a 40 mg/kg, respectively (20 and 17 times the maximum recommended human dose (MRHD) on a mg/m² basis, respectively), have revealed no evidence of teratogenic effects. However, in rats, there was an increase in post-implantation losses in dams treated with mirtazapine. There was an increase in pup death during the first 3 days of lactation and a decrease in pup birth weights. The cause of these deaths is not known. The effects occurred at doses that were 20 times

IRTAZAPINE TABLETS, 15 mg and 30 mg

R only
Rev. J 1/2003

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the MRHD, but not at 3 times the MRHD, on a mg/m² basis. There are no adequate and well controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers

It is not known whether mirtazapine is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when mirtazapine is 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 to 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 in U.S. 6-week controlled clinical trials discontinued treatment due to an adverse experience, compared to 7 percent of the 361 placebo-treated patients in those studies. The most common events (≥1%) associated with discontinuation and considered to be drug related (i.e., those events associated with dropout at a rate at least twice that of placebo) included:

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:

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%) 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, hypertension, pharyngitis, rhinitis, sweating, amblyopia, linitus, 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 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 recurrently, 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 subternal.

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, hyperreflexia, 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.

Social 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 the clinical trials did not reveal any tendency for any drug-seeking behavior, these observations were not systematic and it is not possible to predict on the basis of this limited experience the extent to which a CNS-active drug will be misused, diverted and/or abused once marketed. Consequently, patients should be evaluated carefully for history of drug abuse, and such patients should be observed closely for signs of mirtazapine misuse or abuse (e.g., development of tolerance, increments 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 overdose. No specific antidotes for mirtazapine are known.

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

15 mg Tablets — Yellow, round tablet. One side of the tablet scored in half and debossed with the number "9" on one side of the score and the number "33" on the other. The other side of the tablet is debossed with the number "7207". They are available in bottles of 30 and 100.

30 mg Tablets — Red-brown, round tablet. One side of the tablet scored in half and debossed with the number "9" on one side of the score and the number "33" on the other. The other side of the tablet is debossed with the number "7207". They are available in bottles of 30 and 100.

Storage

Store at controlled room temperature 15° to 30°C (59° to 86°F); [see USP Controlled Room Temperature].

Dispense in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required).

Manufactured by:
TEVA PHARMACEUTICAL IND. LTD.
Jerusalem, 91010, Israel

Manufactured For:
TEVA PHARMACEUTICALS USA
Sellersville, PA 17960

Rev. J 1/2003

76-119
Apr-24-03

Usual Dosage: See package insert for full prescribing information.

Store at controlled room temperature (20° to 25°C (68° to 77°F)). USP Controlled Room Temperature. Dispense in a light-resistant container with a child-resistant closure (as required). **KEEP THIS AND ALL OTHER MEDICATIONS OUT OF THE REACH OF CHILDREN.** TP Iss. 8/2001

Manufactured by: TEVA PHARMACEUTICAL IND. LTD., Jerusalem, 91070, Israel
Manufactured for: TEVA PHARMACEUTICALS USA, Sellersville, PA 19850
322929401101

0093-7206-56

NDC 0093-7206-56
MIRTAZAPINE
Tablets
15 mg

Each tablet contains: Mirtazapine

Rx only

30 TABLETS

TEVA

Usual Dosage: See package insert for full prescribing information.

Store at controlled room temperature (20° to 25°C (68° to 77°F)). USP Controlled Room Temperature. Dispense in a light-resistant container with a child-resistant closure (as required). **KEEP THIS AND ALL OTHER MEDICATIONS OUT OF THE REACH OF CHILDREN.** TP Iss. 8/2001

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0093-7206-01

NDC 0093-7206-01
MIRTAZAPINE
Tablets
15 mg

Each tablet contains: Mirtazapine

Rx only

100 TABLETS

TEVA

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NDC 0093-7207-56
MIRTAZAPINE
Tablets
30 mg

Each tablet contains: Mirtazapine

Rx only

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TEVA

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0093-7207-01

NDC 0093-7207-01
MIRTAZAPINE
Tablets
30 mg

Each tablet contains: Mirtazapine

Rx only

30 mg

TEVA

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Manufactured for: TEVA PHARMACEUTICALS USA, Sellersville, PA 19850

0093-7208-56

NDC 0093-7208-56
MIRTAZAPINE
Tablets
45 mg

Each tablet contains: Mirtazapine

Rx only

45 mg

30 TABLETS

TEVA

Usual Dosage: See package insert for full prescribing information.

Store at controlled room temperature (20° to 25°C (68° to 77°F)). USP Controlled Room Temperature. Dispense in a light-resistant container with a child-resistant closure (as required). **KEEP THIS AND ALL OTHER MEDICATIONS OUT OF THE REACH OF CHILDREN.** TP Iss. 8/2001

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Manufactured for: TEVA PHARMACEUTICALS USA, Sellersville, PA 19850

0093-7208-01

NDC 0093-7208-01
MIRTAZAPINE
Tablets
45 mg

Each tablet contains: Mirtazapine

Rx only

45 mg

100 TABLETS

TEVA

15 pages redacted from this section of
the approval package consisted of draft labeling

**CENTER FOR DRUG
EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

76-119

CSO LABELING REVIEW(S)

SUPERSEDES APPROVAL SUMMARY FOR THE SUBMISSION DATED NOVEMBER 25, 2002
REVIEW OF PROFESSIONAL LABELING
APPROVAL SUMMARY
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: **76-119** Date of Submission: **January 22, 2003**

Applicant's Name: **Teva Pharmaceuticals USA**

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

Satisfactory in FPL as of the November 27, 2001 submission. (Vol 2.1)

Professional Package Insert Labeling:

Satisfactory in FPL as of the January 22, 2003 submission. (Rev. J 1/2003) (Vol. 3.1))

Revisions needed post-approval: The firm needs to submit an amendment with FPL or reference the previously submitted FPL for the 45 mg strength when Mylan's 180 day exclusivity expires.

BASIS OF APPROVAL:

Patent/ Exclusivities

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 Comments: **This application is only approved for the 15 mg and 30 mg strengths.**

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?		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.			
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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
 no exclusivities
 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 Concomittant 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.

- 2. TEVA is the manufacturer.
- 3. The drug product will be made available in container (HDPE) sizes of 30s (CRC) and 100s in all three strengths.
- 4. The inactives are accurately listed in the DESCRIPTION section.(Vol 1.8, p.3860)
- 5. The tablet descriptions are accurate as seen in the HOW SUPPLIED section.
- 6. 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 Controlled Room Temperature].
USP – not USP

7. 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 in the USP, with a child-resistant closure (as required).
USP – not USP
8. Scoring:
NDA – 15 mg and 30 mg – scored
ANDA - 15 mg and 30 mg – scored
9. TEVA is eligible for 180 day exclusivity of the 15 mg and 30 mg strengths only. Mylan believes they are the first to file a paragraph IV for the 45 mg strength and would be entitled to 180 exclusivity. This approval summary is only addressing the 15 mg and 30 mg strengths. The firm will need to submit an amendment or reference the previously submitted FPL for the 45 mg strength when the 180 day exclusivity for the 45 mg expires for Mylan.

Date of Review: 01-23-03

Date of Submission: 01-22-03

Primary Reviewer: Michelle Dillahunt

Date: 1/23/03

Team Leader: Lillie Golson

Date: 1/23/02

cc: ANDA: 76-119
DUP/DIVISION FILE
HFD-613/MDillahunt/LGolson (no cc)
V:\FIRMSNZ\TEVA\LTRS&REV\76119AP2.L
Review

APPEARS THIS WAY
ON ORIGINAL

SUPERSEDES APPROVAL SUMMARY DATED JULY 15, 2002
REVIEW OF PROFESSIONAL LABELING
APPROVAL SUMMARY
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: **76-119** Date of Submission: **November 25, 2002**
 Applicant's Name: **Teva Pharmaceuticals USA**
 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**

Satisfactory in FPL as of the November 27, 2001 submission. (Vol 2.1)

Professional Package Insert Labeling:

Satisfactory in FPL as of the November 25, 2002 submission. (rev. 11/2002) (Vol. 3.1))

Revisions needed post-approval: **None**

BASIS OF APPROVAL:

Patent/ Exclusivities

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 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?		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
no exclusivities
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 Concomittant 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.

2. TEVA is the manufacturer.

3. The drug product will be made available in container (HDPE) sizes of 30s (CRC) and 100s in all three strengths.

4. The inactives are accurately listed in the DESCRIPTION section.(Vol 1.8, p.3860)

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

6. 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 Controlled Room Temperature].
USP – not USP
7. 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 in the USP, with a child-resistant closure (as required).
USP – not USP
8. Scoring:
NDA – 15 mg and 30 mg – scored --- 45 mg - unscored
ANDA - 15 mg and 30 mg – scored --- 45 mg - unscored

Date of Review: 12-30-02

Date of Submission: 11-25-02

Primary Reviewer: Michelle Dillahunt

Date: 1/8/03

Team Leader: Little Golson

Date: 1/8/03

cc: ANDA: 76-119
DUP/DIVISION FILE
HFD-613/MDillahunt/LGolson (no cc)
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Review

APPEARS THIS WAY
ON ORIGINAL

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

Approved by AP Summary for Nov 25, 2002 Submission

ANDA Number: 76-119

Date of Submission: July 5, 2002

Applicant's Name: TEVA Pharmaceuticals USA

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?

Container Labels: 30s and 100s

Satisfactory in FPL as of November 27, 2001 submission. (Vol 2.1)

Professional Package Insert Labeling:

Satisfactory in FPL as of July 5, 2002 submission (Vol 3.1 - Rev. F 7/2002)

Revisions needed post-approval: - PI - HOW SUPPLIED - state that the 45 mg tablet is unscored

BASIS OF APPROVAL:

Patent/ Exclusivities

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, INDICATIONS AND USAGE 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)
 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®, approved 4/9/02 (IN DRAFT).
2. Patent/ Exclusivities:
two patents – 5977099 – 6/16/17
6399310 -- 2/12/21
The firm has filed a Paragraph IV certification to both patents. The second patent is not listed in the Orange Book yet.
One exclusivity (M-18) [expires 4-9-05] for the use of this drug product for maintenance therapy.
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. ADVERSE REACTIONS
 - i. ECG Changes subsection revised
 - ii. New subsection added as last subsection.
 - d. DOSAGE AND ADMINISTRATION
Maintenance/Extended Treatment subsection revised.
3. TEVA is the manufacturer.
4. The drug product will be made available in container sizes of 30s (CRC) and 100s in all three strengths.

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 Controlled Room Temperature].
 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 in the USP, with a child-resistant closure (as required).
 USP – not USP
9. Scoring:
 NDA – 15 mg and 30 mg – scored --- 45 mg - unscored
 ANDA - 15 mg and 30 mg – scored --- 45 mg - unscored

Date of Review: 7-12-02

Date of Submission: 7-5-02

Primary Reviewer: Adolph Vezza

Date: 7-15-02

Team Leader: Lillie Golson

Date: 7/13/02



cc: ANDA: 76-119
 DUP/DIVISION FILE
 HFD-613/AVezza/LGolson (no cc)
 aev/7/12/02\V:\FIRMSNZ\TEVAL\TRS&REV\76119.APL
 Review

APPEARS THIS WAY
 ON ORIGINAL

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

ANDA Number: **76-119**

Dates of Submission: **May 1 and May 20, 2002**

Applicant's Name: **TEVA Pharmaceuticals USA**

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

Labeling Deficiencies:

INSERT

1. PRECAUTIONS

General, Use in Patients with Concomitant Illness, second paragraph - Add the following as the second sentence:

"... heart disease. Mirtazapine was not associated with clinically significant ECG abnormalities in U.S. and non-U.S. placebo controlled trials. Mirtazapine was ..."

2. DOSAGE AND ADMINISTRATION

Maintenance/Extended Treatment - Add the following as the first sentence:

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 ...

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/rid/labeling_review_branch.html

**APPEARS THIS WAY
ON ORIGINAL**

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

**APPEARS THIS WAY
ON ORIGINAL**

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

Do you have 12 Final Printed Labels and Labeling?

Container Labels: 30s and 100s

Satisfactory in FPL as of November 27, 2001 submission. (Vol 2.1)

Professional Package Insert Labeling:

Revisions needed post-approval: -

BASIS OF APPROVAL:

Patent/ Exclusivities

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)

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)

- Review based on the labeling of Remeron®, approved 4/9/02 (IN DRAFT).
- Patent/ Exclusivities:
one patent – 5977099 – 6/16/17
The firm has filed a Paragraph IV certification to the patent.
One exclusivity (M-18) [expires 4-9-05] for the use of this drug product for maintenance therapy.

3. TEVA is the manufacturer.
4. The drug product will be made available in container sizes of 30s (CRC) and 100s in all three strengths.
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 Controlled Room Temperature].
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 in the USP, with a child-resistant closure (as required).
USP – not USP
9. Scoring:
NDA – 15 mg and 30 mg – scored --- 45 mg - unscored
ANDA - 15 mg and 30 mg – scored --- 45 mg - unscored

Date of Review: 7-3-02

Dates of Submission: 5-1 and 5-20-02

Primary Reviewer: Adolph Vezza

Date:

7-5-02

Team Leader: Lillie Golson

Date:

7/5/02

cc: ANDA: 76-119
DUP/DIVISION FILE
HFD-613/AVezza/LGolson (no cc)
aev/7/3/02[V:\FIRMSNZ\TEVA\LTRS&REV\76119na2.l
Review

APPEARS THIS WAY
ON ORIGINAL

(supersedes tentative approval summary dated 9-20-01)
TENTATIVE APPROVAL SUMMARY
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 76-119

Date of Submission: November 27, 2001

Applicant's Name: TEVA Pharmaceuticals USA

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 and 100s

Satisfactory in FPL as of November 27, 2001 submission.

Professional Package Insert Labeling:

Satisfactory in FPL as of November 27, 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).			
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?			
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?			
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?			
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?			
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.		X	

FOR THE RECORD: (portions taken from previous review)

- Review based on the labeling of Remeron®, revised 3/99; approved 8/30/00.
- Patent/ Exclusivities:
one patent – 5977099 – 6/16/17
The firm has filed a Paragraph IV certification to the patent.
- TEVA is the manufacturer.
- The drug product will be made available in container sizes of 30s (CRC) and 100s in all three strengths.

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 Controlled Room Temperature].
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 in the USP, with a child-resistant closure (as required).
USP – not USP
9. Scoring:
NDA – 15 mg and 30 mg – scored --- 45 mg - unscored
ANDA - 15 mg and 30 mg – scored --- 45 mg - unscored

Date of Review: 1-4-02

Date of Submission: 11-27-01

Primary Reviewer: Adolph Vezza *IS*

Date: 1/7/02

Team Leader: Charlie Hoppes *CH*

Date: 1/7/02

cc: ANDA: 76-119
DUP/DIVISION FILE
HFD-613/AVezza/CHoppes (no cc)
aev/1/4/02|V:\FIRMSNZ\TEVALTRS&REV\76119TAP2.L
Review

APPEARS THIS WAY
ON ORIGINAL

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

ANDA Number: **76-119**

Date of Submission: **September 10, 2001**

Applicant's Name: **TEVA Pharmaceuticals USA**

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 and 100s

Satisfactory, in draft, as of September 10, 2001 submission.

Professional Package Insert Labeling:

Satisfactory, in draft, as of September 10, 2001 submission.

Revisions needed post-approval: - differentiate the product strengths on the container labels

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).			
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		X	
Is the scoring configuration different than the RLD?			
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?			
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.		X	

FOR THE RECORD:

1. Review based on the labeling of Remeron®, revised 3/99; approved 8/30/00.
2. Patent/ Exclusivities:
one patent – 5977099 – 6/16/17
The firm has filed a Paragraph IV certification to the patent.
3. TEVA is the manufacturer.
4. The drug product will be made available in container sizes of 30s (CRC) and 100s in all three strengths.

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 Controlled Room Temperature].
 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 in the USP, with a child-resistant closure (as required).
 USP – not USP
9. Scoring:
 NDA – 15 mg and 30 mg – scored --- 45 mg - unscored
 ANDA - 15 mg and 30 mg – scored --- 45 mg - unscored

Date of Review: 9-19-01

Date of Submission: 9-10-01

Primary Reviewer: Adolph Vezza *AV*

Date:

9/20/01

Team Leader: Charlie Hoppes *CH*

Date:

9/20/01

cc: ANDA: 76-119
 DUP/DIVISION FILE
 HFD-613/AVezza/CHoppes (no cc)
 aev/9/19/01|V:\FIRMSNZ\TEVA\LTRS&REV\76119TAP.L
 Review

APPEARS THIS WAY
 ON ORIGINAL

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

ANDA Number: 76-119

Date of Submission: February 26, 2001

Applicant's Name: TEVA Pharmaceuticals USA

Established Name: Mirtazapine Tablets, 15 mg, 30 mg, and 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 Controlled Room Temperature].

2. CONTAINER 30s and 100s

a. See GENERAL COMMENT above.

b. We encourage you to further differentiate your tablet strengths by boxing, contrasting colors, or some other means.

3. INSERT

a. GENERAL COMMENTS

i. "In vitro" and "in vivo" should be in *italic* print throughout the text of the insert.

ii. We encourage you to use the word "to" instead of a , when expressing a range, particularly a dosage range.

b. TITLE

We encourage you to place "Rx only" immediately beneath the title.

c. DESCRIPTION

i. Indicate the botanical source of the starch ("corn").

ii. Include the ingredients of the

d. CLINICAL PHARMACOLOGY

i. Pharmacodynamics, fourth paragraph – "H₁" rather than

ii. Pharmacokinetics, last sentence – "mcg" rather than

e. PRECAUTIONS

General

- i. Increased Appetite/Weight Gain, second sentence – "... of \geq 7% of body ..."
- ii. Cholesterol/Triglycerides
 - A). First sentence – " \geq 20%"
 - B). Last sentence – " \geq 500 mg/dl"

f. DOSAGE AND ADMINISTRATION

Initial Treatment, last sentence – "Mirtazapine has ..." (upper case "M")

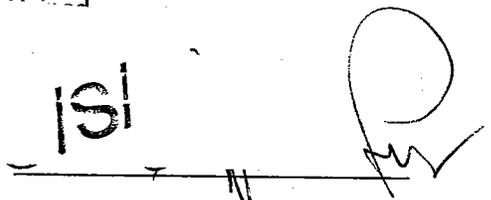
g. HOW SUPPLIED

- i. See GENERAL COMMENT (1) above.
- ii. We encourage you to utilize the NDC numbers in this section.

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



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 and 100s

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.			

FOR THE RECORD:

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

one patent – 5977099 – 6/16/17
one exclusivity – NCE – 6/14/01

The firm has filed a Paragraph IV certification to the patent.
3. TEVA is the manufacturer.
4. The drug product will be made available in container sizes of 30s (CRC) and 100s in all three strengths.
5. The inactives are accurately listed in the DESCRIPTION section except the firm has failed to list the botanical source of the starch and the ingredients of the _____
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, between 15o and 30oC (59o and 86oF); [see USP Controlled Room Temperature].
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 in the USP, with a child-resistant closure (as required).
USP – not USP
9. Scoring:
NDA – 15 mg and 30 mg – scored — 45 mg - unscored
ANDA - 15 mg and 30 mg – scored — 45 mg - unscored

Date of Review: 3-26-01

Date of Submission: 2-26-01

Primary Reviewer: Adolph Vezza

ISI

Date:

3/27/01

Team Leader: Charlie Honnes

ISI

Date:

3/27/01

cc: ANDA: 76-119
DUP/DIVISION FILE
HFD-613/AVezza/CHoppes (no cc)
aev/3/26/01|V:\FIRMSNZ\TEVALTRS&REV76119na1.l
Review

APPEARS THIS WAY
ON ORIGINAL

**CENTER FOR DRUG
EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

76-119

CHEMISTRY REVIEW(S)

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

1. CHEMISTRY REVIEW NO. 1
2. ANDA # 76-119
3. NAME AND ADDRESS OF APPLICANT
TEVA Pharmaceuticals USA
1090 Horsham Road
P.O. Box 1090
North Wales, PA 19454
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 26, 2001
FDA Acceptable for filing: February 26, 2001
Labeling Deficiency Letter: March 27, 2001
Bioequivalency Telephone Amendment: April 12, 2001
10. PHARMACOLOGICAL CATEGORY Treatment of depression
11. Rx or OTC Rx

APPEARS THIS WAY
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12. RELATED DMF(s)

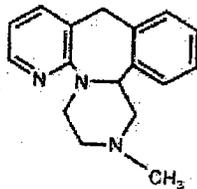
DMF #	LOA page #	Component	Manufacturer
	3870	Mirtazapine	Teva-Tech Ltd.
	4402	_____	_____
	4404, 4455	_____	_____
	4410	_____	_____
	4428	_____	_____
	4427	_____	_____
	4454	_____	_____
	4478	_____	_____
	4482	_____	_____
	4499	_____	_____
	4502	_____	_____
	4497	_____	_____

13. DOSAGE FORM Tablets

14. POTENCIES 15 mg, 30 mg 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 C₁₇ H₁₉ N₃. 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 following sections of the ANDA were found to be deficient regarding chemistry, manufacturing and controls information:

- DMF —, Mirtazapine from Teva-Tech Ltd. was reviewed in conjunction with the ANDA and found to be deficient
- API specifications require revision
- Description of the reference standard is unclear
- Source of container pigment is unclear
- Identification of degradants and impurities and validation of the HPLC method requires additional information
- Bioequivalence has requested revision of dissolution specifications
- Finished product specifications require revision

18. CONCLUSIONS AND RECOMMENDATIONS: Not Approvable-Minor

19. REVIEWER: Susan Zuk

DATE COMPLETED: 6/4/01

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

1. CHEMISTRY REVIEW NO. 2
2. ANDA # 76-119
3. NAME AND ADDRESS OF APPLICANT
TEVA Pharmaceuticals USA
1090 Horsham Road
P.O. Box 1090
North Wales, PA 19454
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 26, 2001
FDA Acceptable for filing: February 26, 2001
Bioequivalence Telephone Amendment: April 12, 2001
Bioequivalence Amendment: May 14, 2001
Minor Amendment: September 10, 2001 (subject of this
Review)
Labeling Amendment: November 27, 2001
Telephone Amendment: December 28, 2001
10. PHARMACOLOGICAL CATEGORY Treatment of depression
11. Rx or OTC Rx

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12. RELATED DMF(s)

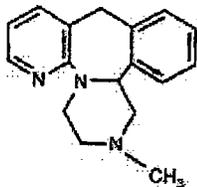
DMF #	LOA page #	Component	Manufacturer
	3870	Mirtazapine	Teva-Tech Ltd.

13. DOSAGE FORM Tablets

14. POTENCIES 15 mg, 30 mg 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 C₁₇H₁₉N₃. Its molecular weight is 265.36. The structural formula is the following and it is the racemic mixture:



16. RECORDS AND REPORTS

The product is non-compendial. A methods validation package has been sent to the district laboratory.

17. COMMENTS:

The ANDA is recommended for tentative approval pending an acceptable inspection report of the finished dosage manufacturer.

- ✓ Bio Evaluation acceptable 5/24/01
- ✓ Labeling acceptable 9/20/01

18. CONCLUSIONS AND RECOMMENDATIONS: Recommend Tentative Approval

19. REVIEWER: Susan Zuk

DATE COMPLETED: 11/8/01
revised 1/2/02

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

1. CHEMISTRY REVIEW NO. 3
2. ANDA # 76-119
3. NAME AND ADDRESS OF APPLICANT
TEVA Pharmaceuticals USA
1090 Horsham Road
P.O. Box 1090
North Wales, PA 19454
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 26, 2001
FDA Acceptable for filing: February 26, 2001
Bioequivalence Telephone Amendment: April 12, 2001
Bioequivalence Amendment: May 14, 2001
Minor Amendment: September 10, 2001
Labeling Amendment: November 27, 2001
Telephone Amendment: December 28, 2001
Tentative Approval: January 15, 2002
90-Day Amendment: April 5, 2002
Telephone Amendment re: MV: April 23, 2002
Labeling Amendment: May 1, 2002
Labeling Amendment: May 20, 2002
Labeling Amendment: July 5, 2002
10. PHARMACOLOGICAL CATEGORY Treatment of depression
11. Rx or OTC Rx

12. RELATED DMF(s)

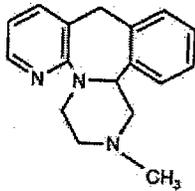
DMF #	LOA page #	Component	Manufacturer
	3870	Mirtazapine	Teva-Tech Ltd.

13. DOSAGE FORM Tablets

14. POTENCIES 15 mg, 30 mg 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 C₁₇H₁₉N₃. Its molecular weight is 265.36. The structural formula is the following and it is the racemic mixture:



16. RECORDS AND REPORTS

The product is non-compendial. A methods validation package was sent to the district laboratory; acceptable 4/23/02 - see Section 31.

17. COMMENTS:

The ANDA is recommended for tentative approval pending an acceptable inspection report of the finished dosage manufacturer.

- ✓ Bio Evaluation acceptable 5/24/01
- ✓ Labeling acceptable 7/15/02

18. CONCLUSIONS AND RECOMMENDATIONS: Recommend Tentative Approval (2nd TA)

19. REVIEWER: Susan Zuk

DATE COMPLETED: 11/8/01
revised 1/2/02, 4/25/02; 7/25/02

This review was revised 7/25/02 to add information provided in the 4/5/02 amendment which was overlooked in the 4/25/02 draft review. Refer to the raw materials section of this review.

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

1. CHEMISTRY REVIEW NO. 4
2. ANDA # 76-119
3. NAME AND ADDRESS OF APPLICANT
TEVA Pharmaceuticals USA
1090 Horsham Road
P.O. Box 1090
North Wales, PA 19454
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 26, 2001
FDA Acceptable for filing: February 26, 2001
Bioequivalence Telephone Amendment: April 12, 2001
Bioequivalence Amendment: May 14, 2001
Minor Amendment: September 10, 2001
Labeling Amendment: November 27, 2001
Telephone Amendment: December 28, 2001
Tentative Approval: January 15, 2002
90-Day Amendment: April 5, 2002
Telephone Amendment re: MV: April 23, 2002
Labeling Amendment: May 1, 2002
Labeling Amendment: May 20, 2002
Labeling Amendment: July 5, 2002
Labeling Amendment: November 25, 2002
Minor Amendment - Final Approval Requested: 1/7/03
Labeling Amendment: January 22, 2003
10. PHARMACOLOGICAL CATEGORY Treatment of depression
11. Rx or OTC Rx

12. RELATED DMF (s)

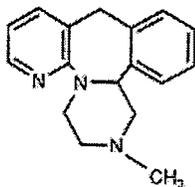
DMF #	LOA page #	Component	Manufacturer
—	3870	Mirtazapine	Teva-Tech Ltd.

13. DOSAGE FORM Tablets

14. POTENCIES 15 mg, 30 mg 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 C₁₇ H₁₉ N₃. Its molecular weight is 265.36. The structural formula is the following and it is the racemic mixture:



16. RECORDS AND REPORTS

The product is non-compendial. A methods validation package was sent to the district laboratory; acceptable 4/23/02 - see Section 31.

17. COMMENTS:

The ANDA is recommended for approval. The 1/7/03 amendment was submitted to inform OGD that the firm formally requests approval. The ANDA received a 2nd tentative approval 10/8/02. No changes have been made to the control documentation submitted in the ANDA since the 2nd TA. The court ruled in favor of the applicant on 12/18/02 and the final printed label insert was provided to OGD 11/25/02.

- Bio Evaluation acceptable 5/24/01
- Labeling acceptable 7/15/02
- EER for Finished Dosage acceptable 1/3/02

18. CONCLUSIONS AND RECOMMENDATIONS: Recommend Approval

19. REVIEWER: Susan Zuk

DATE COMPLETED: 1/15/03

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**CENTER FOR DRUG
EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

76-119

**BIOEQUIVALENCE
REVIEW(S)**

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: #76-119

APPLICANT: Teva 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.

We acknowledge that the following dissolution testing has been incorporated into your stability and quality control programs:

The dissolution testing should be conducted in 900 mL of 0.1 N HCL at 37°C using USP Apparatus 2 (Paddle) at 50 rpm.

The test product should meet the following specifications as recommended by the Agency:

Not less than 0.9 (Q) of the labeled amount of mirtazapine 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,

fr


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

Mirtazapine Tablets
15, 30, 45 mg
ANDA #76-119
Reviewer: Lin-Whei Chuang
V:\FIRMSNZ\TEVA\LTRS&REV\76119SDW.201

Teva Pharmaceuticals USA
North Wales, PA
Submission Dated:
February 26, 2001
April 12, 2001
May 14, 2001

Review of a Fasting and a Non-Fasting BE Studies,
Dissolution Data, and Waiver Request

Background:

Reference Listed Drug (RLD):

Remeron® 15 mg tablets (mirtazapine 15 mg tablets) of Organon Inc. (approved through NDA #20-415 on 6/14/96) is currently the designated RLD in the Orange Book of 2001.

Before 12/00, the designated RLD was Remeron® 45 mg tablets but was changed to the 15 mg strength (see Cumulative Supplement 12 of 12/00) due to reported adverse events resulted from the administration of the 45 mg tablets. The firm conducted both fasting and food studies on the 45 mg tablets because its study protocols for its 45 mg tablets were approved by the IRB on 11/14/00 and the study was initiated on 11/18/00, both before the change of RLD.

Currently there are no approved generic products of mirtazapine. This is a first-generic application.

Pharmacology:

Mirtazapine is a noradrenergic and specific serotonergic antidepressant indicated for the treatment of depression.

Pharmacokinetics:

After an oral dose of mirtazapine, the T_{max} is about 2 hours. The elimination half-life is about 20-40 hours. Mirtazapine displays linear kinetics over the dosing range of 15-80 mg/day. The usual effective dosing range is 15-45 mg/day.

The PK of mirtazapine appears to be enantioselective, resulting in higher plasma concentrations and longer half-life of (R)-(-)-enantiomer compare with that of the (S)-(+)-enantiomer.

Metabolites:

Mirtazapine is extensively metabolized after oral administration. Major pathways of biotransformation are demethylation and hydroxylation followed by glucuronide conjugation. As indicated in NDA #20-415, only N-demethyl mirtazapine was found to be pharmacologically active at very low levels in human plasma. Therefore the quantitation of metabolites of mirtazapine is not requested for the BE studies (Control Doc. #00-290).

Food Effect:

Food has little effect on plasma mirtazapine levels, but does delay Tmax.

Submission Contents:

1. The firm conducted a fasting and a non-fasting BE studies on the 45 mg tablets; dissolution testing on all 3 strengths, and waiver request for its 15 mg and 30 mg tablets (submitted on 2/26/01).
2. Two telephone amendments regarding long-term freezer stability data and dissolution testing were submitted on 4/12/01 and 5/14/01, respectively.

Comparative Formulations:

The formulation data submitted by the firm (see attached copy from p. 117, Vol. 1.1) indicated that all 3 strengths of test product are proportionally similar per definition 1 of the general BA/BE guidance.

Fasting Bioequivalence Study - 1 x 45 mg:**Objective:**

To compare the relative bioavailability of Teva's mirtazapine 45 mg tablets with that of Remeron® 45 mg tablets of Organon Inc. in healthy non-smoking adults under fasting conditions.

Design and IRB Approval:

Single-dose, randomized, two-treatment, two-period crossover study in 40 healthy subjects (no alternates). Protocol #B006530 and informed consent form were approved by Novum Independent Institutional Review Board on 11/14/00.

Sites, Dates, and Principal Investigator:

Clinical: _____

11/17-23/00 (period 1)

12/1-7/00 (period 2)

Analytical: _____

1/13-29/01

The maximal storage period for the study samples was 72 days.

Pharmacokinetic and Statistical: _____

Washout Interval:

14 days.

Subject Inclusion:

Forty non-smoking male subjects (24 Blacks, 15 Caucasians, and 1 Asian) were selected based on the screening procedure conducted within 28 days prior to the study as described in the protocol (p.222-224, Vol. 1.2). They had mean age of 32 years (18-46 years), mean height of 70 inches (66-76 inches), and mean weight of 166 lb. (137-200 lb.).

Restriction:

Subjects were instructed of the restrictions stated in the protocol (p. 224-225, Vol. 1.2).

Treatments:

Subjects fasted overnight before receiving one of the following drug treatments with 240 mL of water in the morning of 11/18/00 according to the randomly assigned sequence (AB for #1, 4, 6, 8, 11, 16, 17, 19, 20, 22, 23, 25, 27-29, 32, 33, 35, 36, 40; and BA for the rest of subjects):

Treatment A - Test Drug: One mirtazapine 45 mg tablet,
Teva Pharmaceutical Ltd.; batch
#K-26727, manufacture date
9/24/00, potency 98.5%, batch size
_____ tablets.

Treatment B - Reference Drug: One Remeron® 45 mg tablet,
Organon, Inc.; lot
#0059271293, potency 101.9%,
expires 6/01.

In the morning of 12/2/00, subjects received the alternate treatment.

Post-dose Procedure:

1. Subjects remained fasted for 4 hours post-dose.
2. Subjects remain ambulatory for 4 hours post-dose in period 1, but remained in bed for 4 hours post-dose because of adverse events experienced in period 1 (syncope, dizziness, drowsiness, and low BP).
3. Urine drug screens were performed at check-in of each period.
4. Blood pressure and pulse rate were measured at 2, 48, and 120 hours post-dose.
5. Fluids were restricted from 1 hour before to 1 hour after dosing except water administered with the study drug.
6. Blood samples were drawn at 0, 0.5, 1, 1.33, 1.67, 2, 2.33, 2.67, 3, 3.33, 3.67, 4, 6, 8, 12, 16, 24, 48, 72, 96, and 120 hours after dosing. Plasma samples were stored at -22°C pending assay of mirtazapine.
7. Physical examination and medical history were performed at the end of period 2.
8. Subjects were allowed to leave the clinical facility after the 48-hour blood draw, and returned for the subsequent blood draws.

Study Drug Accountability:

All unused drugs were retained at the clinical site in accordance with Agency's requirements (21 CFR, Sections 320.38 and 320.63).

Analytical Methodology:

[]
below in Tables 1-2.

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Protocol Deviations:

1. #20 reported using OTC hydrocortisone cream 3 days before period 1.
2. #38 reported taking an aspirin 5 days before period 1.
3. #40 reported eating chocolate cake at 15.5 hours before dosing of period 1.

All above deviations were reviewed by the investigator and subjects were approved to continue in the study.

Adverse Events:

Total # of events	Treatment A	Treatment B
# definitely or probably related to the study drug ^{a,b}	46	52
	45	50

a = Nature of these complaints: syncope, elevated ALT, BP, temperature, urea nitrogen, platelet sufficiency, or platelet count, lightheaded, tired, decreased pulse or BP, chills, nausea, euphoria, swollen hands, protein I urine, abdominal cramping or pain, or leg cramps.

b = They were judged to be mostly mild, and occasionally moderate in nature.

Plasma Concentration and Pharmacokinetic Analysis

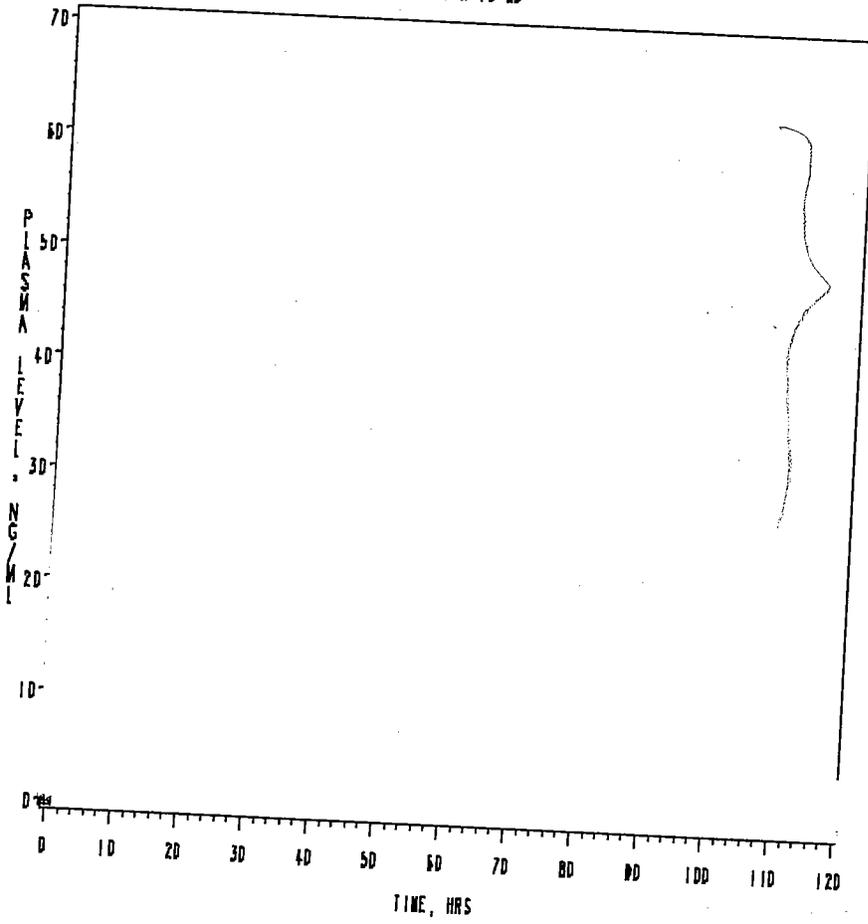
A total of 1630 plasma samples from 39 subjects were assayed for mirtazapine in 24 batches of assay. Eight (8) samples were not received at the clinical site due to 'No Sample' in the clinical report. None of these 8 samples was adjacent to the T_{max}. A total of 69 samples were repeated because of high or low internal standard response, above quantifiable limit, low standard eliminated, unknown processing error, or peak in 0-hour sample. None of them was repeated due to pharmacokinetic anomaly. One sample was not reportable due to low internal standard response after repeats. This sample was not adjacent to T_{max}.

The mean plasma concentrations of mirtazapine at each sampling time point after both treatments are presented in Figure 1. The same data and the mean pharmacokinetic parameters of mirtazapine are presented in Tables 3-4.

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FIG 1: PLASMA MIRTAZAPINE LEVELS

MIRTAZAPINE TABLETS, 1X45 MG, ANDA #76-119
UNDER FASTING CONDITIONS
DDSE=1 X 45 MG



TRT ***1 BBB 2
1=TEST(TEVA) 2=REF(ORGANON)

**TABLE 3: ARITHMETIC MEAN PLASMA MIRTAZAPINE CONCENTRATIONS [ng/mL]
VERSUS TIME AFTER 1 X 45 MG TABLET UNDER FASTING CONDITIONS
(N=39 EXCEPT WHEN INDICATED)**

	TEST MEAN	SD	REF. MEAN	SD	TEST/REF.
TIME HR					
0	0.000	0.000	0.000	0.000	
0.5	6.978	10.639	7.760	24.235	
1	44.024	30.347	40.267	24.569	0.899
1.33	53.572	22.468	58.140	32.174	1.093
1.67	54.485	16.783	55.431	19.761	0.921
2	58.577	19.717	60.833	25.127	0.983
2.33	58.638	19.489	61.131	21.690	0.963
2.67	57.292	20.947	57.723	17.927	0.959
3	54.877	18.715	54.366	17.145	0.993
3.33	51.410	16.712	54.931A	17.290	1.009
3.67	50.544	17.233	52.697B	14.662	0.936
4	49.186B	16.302	51.810	16.097	0.959
6	35.882	12.537	37.695	12.174	0.949
8	28.084	9.325	29.662	9.260	0.952
12	17.675	6.425	19.220	6.787	0.947
16	13.009	4.895	14.458	5.245	0.920
24	9.030	3.667	9.985	3.967	0.900
48	3.721	1.925	4.010	1.913	0.904
72	1.790	1.008	2.020	1.191	0.928
96	1.089B	0.802	1.157B	0.773	0.886
120	0.509	0.652	0.548	0.562	0.941
					0.930

A = (N=38), B = (N=37)

**TABLE 4: ARITHMETIC MEANS OF PHARMACOKINETIC PARAMETERS FOR MERTAZAPINE
IN 39 SUBJECTS AFTER 1X45 MG TABLET UNDER FASTING CONDITIONS**

	TEST MEAN	SD	REF. MEAN	SD	TEST/REF.
PARAMETER					
AUCI (NG*HR/ML)	870.026	310.132	930.359	310.457	0.935
AUCT (NG*HR/ML)	834.000	297.961	898.128	302.959	0.929
C _{MAX} (NG/ML)	72.713	25.375	74.405	28.384	0.977
KE	0.031	0.009	0.031	0.008	0.998
LAUCI	822.203a	0.335c	884.553a	0.318c	0.930b
LAUCT	787.437a	0.338c	852.959a	0.321c	0.923b
LC _{MAX}	68.886a	0.329c	70.153a	0.334c	0.982b
THALF (HR)	24.550	7.494	24.049	6.450	1.021
T _{MAX} (HR)	2.111	1.031	2.183	0.948	0.967

a = GEOMETRIC MEANS

b = RATIO OF GEOMETRIC MEANS

c = SD OF LOG-TRANSFORMED PARAMETERS

Statistical Analysis:

ANOVA was conducted by the firm on the non-transformed and log-transformed AUCT, AUCI and CMAX of mirtazapine. The model included sequence, subject within sequence, treatment and period as factors. The sequence effect was tested using sub(seq) mean square as an error term. All other effects were tested against the residual error from the ANOVA. ANOVA showed significant treatment effects in LNAUT (p=0.007) and LNAUCI (p=0.0117). Results presented in Table 5 were from ANOVA conducted by the reviewer which are identical to those reported by the firm:

TABLE 5: LEAST-SQUARES MEANS AND 90% CONFIDENCE INTERVALS FOR MIRTAZAPINE PHARMACOKINETIC PARAMETERS AFTER 1X45 MG TABLET UNDER FASTING CONDITIONS

PARAMETER	TEST LSM	REF. LSM	TEST/REF.	90% CONF. INT.	Root MSE ^a
AUCI [ng·hr/mL]	869.00	929.88	0.93	89.29 - 97.62	--
AUCT [ng·hr/mL]	832.93	897.64	0.93	88.53 - 97.05	--
CMAX [ng/mL]	72.45	74.51	0.97	89.30 - 105.20	--
LAUCI (Geometric mean)	820.83	883.78	0.93	88.89 - 97.04	0.114949
LAUCT (Geometric mean)	786.04	852.17	0.92	88.16 - 96.51	0.118246
LCMAX (Geometric mean)	68.63	70.20	0.98	91.04 - 104.98	0.186456

a = From ANOVA Table

Comments on Results of Fasting Bioequivalence Study:

1. The computation of pharmacokinetic parameters and the 90% confidence intervals conducted by the firm has been confirmed by the reviewer using data submitted in the data diskette. The 90% confidence intervals of LNAUCT, LNAUCI and LNCMAX are all within the acceptable range of 80-125%.
2. Results of this fasting bioequivalence study are acceptable.

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Non-Fasting Bioequivalence Study - 1 x 45 mg:

Objective:

To compare the relative bioavailability of Teva's mirtazapine 45 mg tablets with that of Organon's Remeron® 45 mg tablets in healthy non-smoking adults under non-fasting conditions; and to compare the bioavailability of Teva's mirtazapine 45 mg tablets under non-fasting and fasting conditions.

Design and IRB Approval:

Single-dose, randomized, 3-treatment, 3-period, 6-sequence study in 24 healthy subjects (no alternates). Protocol #00317 and informed consent form were approved by the Ethics Review Committee of Integrated Research on 11/15/00.

Sites, Dates, and Principal Investigator:

Clinical:

11/19-25/00 (period 1)
12/3-9/00 (period 2)
12/17-23/00 (Period 3)

Analytical:

1/19-2/6/01

The maximal storage period for the study samples was 78 days.

Pharmacokinetic and Statistical:

Washout Interval:

14 days.

Inclusion Criteria of Subjects:

Twenty-four non-smoking male subjects (23 Caucasians and 1 Black) were selected 28 days prior to period 1 based on the inclusion and exclusion criteria as described in the protocol (p.1874-1875, Vol. 1.5). They had mean age of 40 years (18-53 years), mean height of 175.9 cm (164-191.5 cm), and mean weight of 74.6 Kg (61.3-81.5 Kg).

Restriction:

Subjects were instructed of the restrictions stated in the protocol (p. 1875, Vol. 1.5).

Treatments:

Subjects fasted overnight before receiving one of the following drug treatments with 240 mL of water in the mornings of 11/20/00, 12/4/00, and 12/18/00 according to the randomly assigned sequence:

ABC: #6, 8, 13, 22

BCA: #7, 14, 23

CAB: #2, 4, 16, 19

ACB: #11, 17, 20

BAC: #3, 12, 18

CBA: #5, 10, 24

(Subjects #1, 9, 15, 21 received, respectively, treatment B, A, C, B, in period 1 and did not continue. See explanations in results section).

Treatment A - Test Drug: One mirtazapine 45 mg tablet, Teva Pharmaceutical Ltd.; batch #K-26727, given 30 minutes after the initiation of a standard high-fat breakfast*.

Treatment B - Reference Drug: One Remeron® 45 mg tablet, Organon, Inc.; lot #0059271293, given 30 minutes after the initiation of a standard high-fat breakfast*.

Treatment C - Test Drug: One mirtazapine 45 mg tablet, Teva Pharmaceutical Ltd.; lot #K-26727, given under fasting conditions.

* = 1 buttered English muffin, 1 fried egg, 2 strips of bacon, 1 slice of American cheese, 1 serving of hash brown potatoes, 240 mL of whole milk, and 180 mL of orange juice.

Post-dose Procedure:

Same as those for the fasting study except, during all 3 periods, subjects remained seated, did not lie down, for 4 hours post-dose.

Study Drug Accountability:

All unused drugs were retained per regulatory requirements and Teva's request.

Analytical Methodology:

Same analytical method for the fasting study was conducted. The during-study validation are presented below in Table 6.

TABLE 2: DURING STUDY ASSAY VALIDATION - NON-FASTING STUDY

Parameter	Quality Control Samples	Standard Curve Samples
-----------	-------------------------	------------------------

Comments on the Analytical Method:

The method and data presented in this analytical section are acceptable.

Results:

Drop-out:

Six subjects did not complete the study:

1. Subject #1 and #15 (who received treatments B and C, respectively, in period 1) were withdrawn from the study prior to period 2 dosing because the pre-dose vital signs were outside the normal range.
2. Subjects # 3 and #24 (who were assigned the sequence of BAC and CBA, respectively) were withdrawn from the study prior to period 3 dosing because the pre-dose vital signs were outside the normal range.
3. Subjects #9 and #21 (who received treatment A and B, respectively, in period 1) were withdrawn from the study due to vomiting within 4 hours post-dose.

Protocol Deviations:

No significant deviations were reported.

Adverse Events:

Total # of events	Treatment A	Treatment B	Treatment C
# definitely, probably or possibly related to the study drug ^{a,b}	33	33	24
	27	27	21

a = Nature of these complaints: fatigue, nausea, drowsiness, headache, dizziness, sweatiness, vomiting, difficulty to pronounce words, back pain, and hot flushes.

b = They were judged to be mostly mild, and occasionally moderate in nature.

Plasma Concentration and Pharmacokinetic Analysis

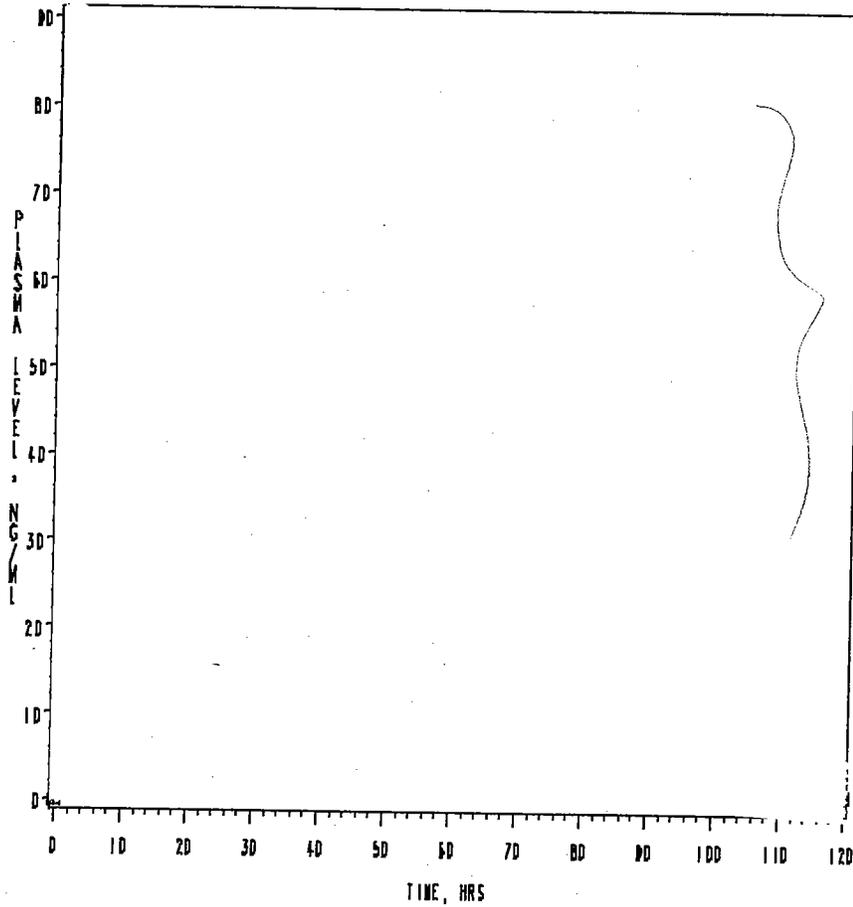
A total of 1133 plasma samples from 18 subjects were assayed for mirtazapine in 21 batches of assay. One (1) sample was not received at the clinical site due to 'No Sample' in the clinical report, it was not adjacent to the Tmax. A total of 124 samples were repeated because above quantifiable limit, low internal standard response, unknown processing error, or peak in 0-hour sample. None of them was repeated due to pharmacokinetic anomaly. However, 20 of these repeated samples were hemolyzed and could not be quantitated. Among these 20 samples, 6 were adjacent to the observed Tmax and were collected from subjects #11 and #12 during treatment A.

The mean plasma concentrations of mirtazapine at each sampling time point after both treatments are presented in Figure 2. The same data and the mean pharmacokinetic parameters of mirtazapine are presented in Tables 7-8.

**APPEARS THIS WAY
ON ORIGINAL**

FIG 2. PLASMA MIRTAZAPINE LEVELS

MIRTAZAPINE TABLETS, 45 MG, ANDA #76-110
UNDER NONFASTING/FASTING CONDITIONS
DDSE=1 X 45 MG



TRT *** 1 ■■■ 2 □□□ 3 ○○○

1=TEST(TEVA) 2=REFERENCE(CORGANDN-FED) 3=TEST(TEVA-FASTING)

**TABLE 7: ARITHMETIC MEAN PLASMA MIRTAZAPINE CONCENTRATIONS [ng/mL]
VERSUS TIME AFTER 1 X 45 MG TABLET UNDER
NON-FASTING AND FASTING CONDITIONS (N=18 EXCEPT WHEN INDICATED)**

TIME HR	TEST-FED	SD	REF.-FED	SD	TEST-FAST	SD	TEST-FED/REF.-FED
0	0.000	0.000	0.000	0.000	0.000	0.000	.
0.5	21.429	29.828	19.623	27.606	23.291	33.460	1.092
1	61.290	47.691	69.051	46.005	83.229a	28.079	0.888
1.33	68.731a	42.819	74.215	39.723	82.717	28.113	0.926
1.67	64.978a	35.011	75.827	39.083	79.972	19.158	0.857
2	63.578b	30.329	72.785a	35.640	79.906b	21.639	0.874
2.33	74.778	38.303	72.145	29.389	75.424a	17.793	1.036
2.67	72.571a	28.223	71.817	24.214	71.518a	15.215	1.010
3	79.439	32.514	74.553a	21.749	73.456	14.854	1.066
3.33	78.571a	36.352	70.094a	24.655	69.822	14.216	1.121
3.67	73.176a	28.002	71.022	19.777	68.078	16.933	1.030
4	71.272	29.029	71.618a	18.594	63.506	14.727	0.995
6	43.519	12.089	52.228	13.096	44.539	11.918	0.833
8	37.671a	18.256	38.322	10.281	33.061	8.518	0.983
12	23.741a	7.514	27.078	8.196	23.550	6.754	0.877
16	19.751	6.686	20.948	5.624	17.331	5.336	0.943
24	12.991	4.338	15.014	4.995	12.211	3.827	0.865
48	6.124	2.889	6.842	3.098	5.249	2.296	0.895
72	3.436	1.916	3.965	2.334	3.110	1.727	0.867
96	1.955	1.295	2.069	1.222	1.690	1.041	0.945
120	1.186	0.964	1.228	0.938	1.031a	0.720	0.965

a = (N=17), b = (n=16)

**TABLE 8: ARITHMETIC MEANS OF PHARMACOKINETIC PARAMETERS OF MIRTAZAPINE
AFTER 1 X 45 MG TABLET UNDER NON-FASTING AND FASTING CONDITIONS
(N=18)**

PARAMETER	TEST-FED	SD	REF.-FED	SD	TEST-FAST	SD	TEST-FED/ REF.-FED	TEST-FED/ TEST-FAST
AUCI	1304.222	515.808	1386.278	439.834	1202.167	346.414	0.941	1.086
AUCT	1247.167	484.075	1330.333	408.642	1153.667	326.376	0.937	1.081
C _{MAX}	101.444	40.514	99.450	28.843	97.567	26.970	1.020	1.040
KE	0.028	0.008	0.028	0.007	0.028	0.008	0.998	0.994
LAUCI	1216.861a	0.382c	1321.164a	0.323c	1154.123a	0.299c	0.921b	1.054b
LAUCT	1165.213a	0.380c	1271.160a	0.315c	1109.402a	0.293c	0.917b	1.050b
LC _{MAX}	93.503a	0.425c	95.363a	0.303c	94.335a	0.263c	0.980b	0.991b
THALF	26.397	5.637	25.941	5.000	26.424	6.565	1.018	0.999
T _{MAX}	2.611	1.300	2.426	1.342	1.685	0.745	1.077	1.550

a = GEOMETRIC MEANS
b = RATIO OF GEOMETRIC MEANS
c = SD OF LOG-TRANSFORMED PARAMETERS

Statistical Analysis:

The firm conducted ANOVA on non-transformed and log-transformed AUCT, AUCI and CMAX of ibuprofen using SAS GLM with model including sequence, subject within sequence, treatment and period as factors. Results presented in Table 9 are from ANOVA conducted by the reviewer which are identical to those reported by the firm.

TABLE 9: LEAST-SQUARES MEAN OF PK FOR MIRTAZAPINE AFTER 1 X 45 MG TABLET UNDER NON-FASTING AND FASTING CONDITIONS (N=18)

	TEST-FED	REF.-FED	TEST-FAST	TEST-FED/ REF.-FED	TEST-FED/ TEST-FAST
PARAMETER					
AUCI (NG*HR/ML)	1246.716	1339.487	1150.014	0.931	1.084
AUCT (NG*HR/ML)	1191.608	1284.689	1103.065	0.928	1.080
CMAX (NG/ML)	100.253	97.829	96.160	1.025	1.043
LAUCI (GEOMETRIC MEAN)	1163.091	1271.953	1107.122	0.914	1.051
LAUCT (GEOMETRIC MEAN)	1113.066	1223.157	1063.623	0.910	1.046
LCMAX (GEOMETRIC MEAN)	92.137	93.584	92.766	0.985	0.993

Comments on Results of Non-Fasting Bioequivalence Study:

1. The computation of pharmacokinetic parameters, LS means, and ratios of means has been confirmed by the reviewer.
2. When comparing the test to reference drugs under fed conditions, the ratios of LS means of LNAUCT, LNAUCI, and LNCMAX are all within the acceptable range of 0.8-1.25.
3. When comparing the test drug under fed to fasting conditions, results in Tables 8&9 showed only slight increase (4-5%) of mean AUC and no change in Cmax. The mean Tmax was delayed from 1.69 hours to 2.61 hours when co-administered with food (Table 8). This is in agreement with RLD's labeling: "Food has little effect on plasma mirtazapine levels, but does delay Tmax".
4. Because subject #11 and #12 had 6 samples not quantifiable near the observed Tmax. The reviewer re-conducted ANOVA without data from these 2 subjects and the outcome of the study remains unchanged.
5. Results of this non-fasting bioequivalence study are acceptable.

IN-VITRO DISSOLUTION TESTING RESULTS:

Mirtazapine is not a USP product. Following is the dissolution method recommended by the Agency (NDA #20-415):

Medium: 900 mL of 0.1 N HCL at 37 ± 0.5 °C
 Apparatus: USP Apparatus 2 (Paddle)
 Paddle Speed: 50 rpm
 Tolerance: NLT — (Q) in 15 minutes.

The firm conducted comparative dissolution testing for the test and reference products using the above method, however, with a different specification. The testing for the 45 mg strength was conducted twice, the second time using a 15-min., instead of a 20-min., time point as requested by DBE (see attached telephone memo of 5/3/01). Results of these testings are presented below in Table 10:

Table 10 : In Vitro Dissolution Testing -						
Drug: Mirtazapine Tablets Dosage Strength: 15 mg, 30 mg, & 45 mg ANDA No: 76-119 Submission Date: 2/26/01 & 5/14/01						
Conditions for Dissolution/Release Testing						
Apparatus: Apparatus II (Paddle) RPM: 50 Medium: 0.1 N HCL Volume: 900 mL No. Units Tested: 12 Tolerance (Q): NLT — in 30 minutes (Firm's Proposal) Reference Drug: Remeron® (Organon Inc.) Assay Methodology: _____						
Results of In Vitro Dissolution						
Sampling Time (min)	Test Product: Mirtazapine Tablets Batch #: K26725 Strength: 15 mg			Reference Product: Remeron® Tablets Lot #: 0799277833 Strength: 15 mg		
	Mean %	Range	% CV	Mean %	Range	% CV
10	94		4.2	93		9.3
20	98		1.3	101		1.9
30	98		1.5	101		1.7
Sampling Time (min)	Test Product: Mirtazapine Tablets Batch #: K26726 Strength: 30 mg			Reference Product: Remeron® Tablets Lot #: 0559256404 Strength: 30 mg		
	Mean %	Range	% CV	Mean %	Range	% CV
10	93		5.2	91		10.9
20	100		1.1	103		2.6
30	100		1.9	104		1.1
Sampling Time (min)	Test Product: Mirtazapine Tablets Batch #: K26727 Strength: 45 mg			Reference Product: Remeron® Tablets Lot #: 0059271293 Strength: 45 mg		
	Mean %	Range	% CV	Mean %	Range	% CV
10	77		9.2	84		12.4
20	98		1.3	103		3.2

30	98	1.1	105	3.1		
Sampling Time (min)	Test Product: Mirtazapine Tablets Batch #: K26727 Strength: 45 mg		Reference Product: Remeron® Tablets Lot #: 0059271293 Strength: 45 mg			
	Mean %	Range	% CV	Mean %	Range	% CV
10	78		9.6	80		6.6
15	92		4.3	96		2.3
30	95		0.8	100		0.9

Comments on Dissolution Tests:

1. Results of all 3 strengths of the test products comply with firm's proposed specification of "NLT —, in 30 minutes", and Agency's recommended specification of "NLT —, in 15 minutes".
2. All 3 strengths of test and reference products are fast-dissolving, i.e., more than — are dissolved within 20 minutes.

Request for Waiver of In Vivo Bioequivalence :

The firm is requesting waiver of the in-vivo bioequivalence study requirements for its 15 mg and 30 mg strengths of the test product based on the fasting and non-fasting *in vivo* bioequivalence studies conducted on the 45 mg strength, the proportionality of formulations, and comparative dissolution data.

Comments on Waiver Request:

1. The fasting and non-fasting bioequivalence studies conducted on the 45 mg strength are acceptable.
2. The dissolution data of all 3 strengths of the test product meet Agency's recommended specification of "NLT — in 15 minutes".
3. The formulations of the 2 lower strengths are proportionally similar to the formulation of the 45 mg tablets.
4. Therefore the waiver for the firm's 15 mg and 30 mg tablets can be granted per 21 CFR 320.22(d) (2).

Recommendation:

1. Both fasting and non-fasting bioequivalence studies conducted by Teva Pharmaceuticals USA on its mirtazapine 45 mg tablet, batch #K-26727, comparing it to Remeron® 45 mg

tablet, lot #0059271293, have been found acceptable by the Division of Bioequivalence. The studies demonstrated that Teva's mirtazapine 45 mg tablet is bioequivalent to the reference product, Remeron® 45 mg Tablet, manufactured by Organon Inc. under fasting and non-fasting conditions.

2. The dissolution tests conducted by Teva Pharmaceuticals USA on its mirtazapine 15 mg, 30 mg and 45 mg tablets, batch #K-26725, #K-26726, and #K-26727, comparing them to Remeron® 15 mg, 30 mg and 45 mg tablets, lot #0799277833, #0559256404 and #0059271293, respectively, have been found acceptable by the Division of Bioequivalence.

The formulations of the 15 mg and 30 mg strengths are both proportionally similar to the 45 mg test product which underwent *in vivo* bioequivalence testing. The waiver of *in vivo* bioequivalence study requirements for the 15 mg and 30 mg tablets is granted per 21 CFR 320.22(d)(2). The 15 mg and 30 mg tablets of the test product are therefore deemed bioequivalent, respectively, to the 15 mg and 30 mg tablets of Remeron® manufactured by Organon Inc..

3. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program and conducted in 900 mL of 0.1 N HCL at 37° C using USP 24 apparatus 2 (paddle) at 50 rpm. The test products should meet the following specifications:

Not less than $\frac{1}{2}$ of the labeled amount of mirtazapine in the dosage form is dissolved in 15 minutes.

Lin-Whei Chuang
Division of Bioequivalence
Review Branch I

RD INITIALLED YHUANG
FT INITIALLED YHUANG

Concur:

ISI *5/18/01*
ISI *5/24/2001*
ISI
Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence

CC: ANDA #76-119
ANDA DUPLICATE
DIVISION FILE
HFD-651/ Bio Drug File
HFD-652/ Lin-Whei Chuang

Endorsements: (Final with Dates)
HFD-652/ L. Chuang *LWC 5/18/01*
HFD-652/ Y. Huang *YH 5/24/2001*
HFD-652/ K. Scardina *KS 5/24/01*
HFD-650/ D. Conner *DC 5/24/2001*

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BIOEQUIVALENCY - ACCEPTABLE submission date: 2/26/01

1. **FASTING STUDY (STF)** *ok* Strength: 45 mg *2/26/01*
Clinical: _____
Analytical: _____
Outcome: AC
2. **FOOD STUDY (STP)** *ok* Strength: 45 mg *2/26/01*
Clinical: _____
Analytical: _____
Outcome: AC
3. **STUDY AMENDMENT (STA)** *ok* submission date: 4/12/01
(Long Term Stability) Strengths: All
Outcome: AC
4. **STUDY AMENDMENT (STA)** submission date: 5/14/01
(Additional Dissolution Data) Strengths: 45 mg
at 15-min. Time Point) *ok* **Outcome: AC**
5. ~~WAIVER (WAI)~~ *ok* Strength: 15 mg *2/26/01*
Dissolution Waiver (Dlw) **Outcome: AC**
6. ~~WAIVER (WAI)~~ *ok* Strength: 30 mg *2/26/01*
Dissolution Waiver (Dlw) **Outcome: AC**

Outcome Decisions: **AC** - Acceptable

WinBio Comments:

**CENTER FOR DRUG
EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

76-119

**ADMINISTRATIVE
DOCUMENTS**

ANDA APPROVAL SUMMARY (Tentative Approval)

ANDA: 76-119

DRUG PRODUCT: Mirtazapine Tablets

FIRM: Teva Pharmaceuticals USA

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

CGMP STATEMENT/EIR UPDATE STATUS: Signed cGMP certifications were provided on pages 3870 for the drug substance manufacturer and 4059 for the drug product manufacturer. An acceptable EER was issued based on profile for the drug substance manufacturer 3/12/01. Inspection of the finished dosage manufacturing facility has been assigned but not yet performed.

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 5/24/01.

METHOD VALIDATION - (DESCRIPTION OF DOSAGE FORM SAME AS FIRM'S): The drug substance and drug product are both non-compendial. A methods validation package has been sent to Diane O'Brien, MV Coordinator.

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 9/20/01.

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

SIZE OF BIO BATCH (FIRM'S SOURCE OF NDS OK?): A common ~~batch~~ designated as batch K-26724 ~~batch~~, was manufactured by Teva Pharmaceuticals Industries Ltd. using drug substances supplied by Teva-Tech, Ltd. The ~~batch~~ was divided into three sub-batches, one batch of each strength. The sub-batches were designated as K-26725 15 mg dosage ~~batch~~, K-26726 30 mg

dosage _____, and K-26727 45 mg dosage _____. 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 _____ tablets (15mg), _____ tablets (30 mg) and _____ tablets (45 mg). The commercial production batch record is the identical to the exhibit batch.

CHEMIST: Susan Zuk
SUPERVISOR: Richard Adams

ISI 12/11/01
ISI 12/17/01

DATE: 11/8/01

DATE:

APPEARS THIS WAY
ON ORIGINAL

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Page(s) of trade

secret and /or

confidential

commercial

information

ANDA 76-119

APPLICANT: Teva Pharmaceuticals USA

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

In accordance with 21 CFR 314.50(d)(1)(i) and (ii)(a), you have provided information regarding your analytical methods and specifications for testing of Mirtazapine and Mirtazapine Tablets. This information was sent to the FDA field laboratory for validation of your test methods. The field laboratory has completed testing and reported its findings to the review chemist. Our analyst found that certain integral information was omitted from your written procedures. We therefore request that you provide the following information as a telephone amendment:

1. The system suitability tests for Assay and Chromatographic Purity of the drug substance do not include precision requirements. We refer you to USP <621>. Please revise the system suitability procedure to require a precision test and provide RSD criteria.
2. Please provide the parameter for ~~_____~~ for the Residual Solvents Test.
3. Please include a precision test and acceptance criteria in your analytical procedure for the ~~_____~~ determination as part of the system suitability testing.
4. Please provide the formula for calculation of total impurities in your procedure for the Degradation and Impurities Test.
5. Please indicate the size of the ~~_____~~ used in the ~~_____~~ for your Dissolution Test procedure.

**APPEARS THIS WAY
ON ORIGINAL**

ANDA APPROVAL SUMMARY

ANDA: 76-119

DRUG PRODUCT: Mirtazapine Tablets

FIRM: Teva Pharmaceuticals USA

DOSAGE FORM: Tablets

STRENGTH: 15, 30 and 45 mg

CGMP STATEMENT/EIR UPDATE STATUS: Signed cGMP certifications were provided on pages 3870 for the drug substance manufacturer and 4059 for the drug product manufacturer. An acceptable EER was issued on 1/3/02.

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 5/24/01.

METHOD VALIDATION - (DESCRIPTION OF DOSAGE FORM SAME AS FIRM'S):

The drug substance and drug product are both non-compendial. A methods validation package has been sent to Diane O'Brien, MV Coordinator. The field lab has completed its evaluation of the analytical methods. This information has been added to the ANDA file.

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 1/23/03.

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

SIZE OF BIO BATCH (FIRM'S SOURCE OF NDS OK?): A common _____ designated as batch K-26724 ' _____) was manufactured by Teva Pharmaceuticals Industries Ltd. using drug substances supplied by Teva-Tech, Ltd. The _____ was divided into three sub-batches, one batch of each strength. The sub-batches were designated as K-26725 15 mg dosage _____ , K-26726 30 mg dosage _____ , and K-26727 45 mg dosage _____ . 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 ~~1~~ tablets (15mg), ~~1~~ tablets (30 mg) and ~~1~~ tablets (45 mg). The commercial production batch record is the identical to the exhibit batch.

CHEMIST: Susan Zuk
SUPERVISOR: Richard Adams

DATE: 1/15/03

DATE:

IS/

IS/ 1/21/03
1/24/03

**APPEARS THIS WAY
ON ORIGINAL**

ANDA APPROVAL SUMMARY (Tentative Approval)

ANDA: 76-119

DRUG PRODUCT: Mirtazapine Tablets

FIRM: Teva Pharmaceuticals USA

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

CGMP STATEMENT/EIR UPDATE STATUS: Signed cGMP certifications were provided on pages 3870 for the drug substance manufacturer and 4059 for the drug product manufacturer. An acceptable EER was issued on 1/3/02.

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 5/24/01.

METHOD VALIDATION - (DESCRIPTION OF DOSAGE FORM SAME AS FIRM'S): The drug substance and drug product are both non-compendial. A methods validation package has been sent to Diane O'Brien, MV Coordinator. The field lab has completed its evaluation of the analytical methods. This information has been added to the ANDA file.

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 7/15/02.

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

SIZE OF BIO BATCH (FIRM'S SOURCE OF NDS OK?): A common _____ designated as batch K-26724 _____ was manufactured by Teva Pharmaceuticals Industries Ltd. using drug substances supplied by Teva-Tech, Ltd. The _____ was divided into three

sub-batches, one batch of each strength. The sub-batches were designated as K-26725 15 mg dosage _____, K-26726 30 mg dosage _____, and K-26727 45 mg dosage _____. 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 _____ tablets (15mg), _____ tablets (30 mg) and _____ tablets (45 mg). The commercial production batch record is the identical to the exhibit batch.

CHEMIST: Susan Zuk

SUPERVISOR: Richard Adams

ISI
10/3/02

DATE: 4/25/02, 7/25/02
DATE: 7/25/02

ISI
10/2/02

**APPEARS THIS WAY
ON ORIGINAL**

MEMORANDUM

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

COMPLETED JUN 20 2002

DATE: June 12, 2002

FROM: Russell Katz, M.D. *RSK, bho/a*
Director
Division of Neuropharmacological Drug Products

SUBJECT: Package Insert Labeling for Approval of
Mirtazapine Abbreviated New Drug Applications

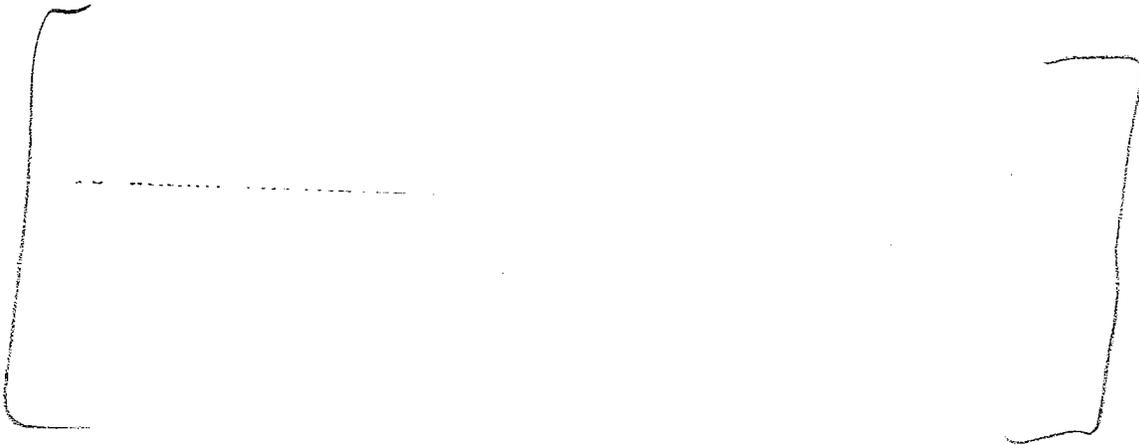
TO: Director, Office of Generic Drugs

The Office of Generic Drugs (OGD) consulted this division regarding acceptable package insert labeling for generic Remeron (mirtazapine) tablets. OGD has asked if the generic firms could carve out the use of Remeron in maintaining a response in patients with major depressive disorder, without compromising safety or effectiveness for the remainder of the non-exclusivity protected uses. This labeling, which was approved on April 9, 2002, was granted 3 years of Hatch/Waxman exclusivity. A meeting was held to address this issue on June 10, 2002.

The meeting included representatives from The Office of Chief Counsel, Office of Generic Drugs, and the Division of Neuropharmacological Drug Products. The recently approved protected additions to the Remeron labeling, and the proposed generic carve-outs were discussed. The meeting participants reviewed each section of the current Remeron package insert and commented on the impact of each proposed deletion on the safety and effectiveness of the drug product. The conclusion reached was that generic firms could carve-out labeling associated with the "use of Remeron in maintaining a response in patients with major depressive disorder" without rendering generic products less safe or effective for all remaining non-protected conditions of use.

Under the approach proposed by OGD and acceptable to this division, the **DOSAGE AND ADMINISTRATION** section of the package insert for generic Remeron (mirtazapine) will have the following changes:

Current Remeron Package Insert without carve-out:

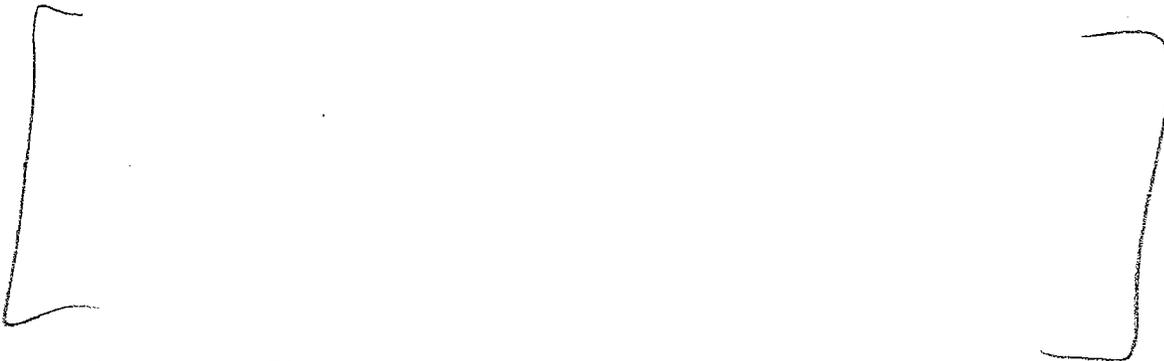


ANDA Labeling with carve-out:

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.

The INDICATIONS AND USAGE section will have the following changes:

Current Remeron labeling without carve-out (3rd & 4th paragraphs):



ANDA labeling with carve-out (3rd & 4th paragraphs):

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.

The **CLINICAL PHARMACOLOGY** section that addresses the results from a longer-term study (last paragraph) will be carved-out. The following are the proposed changes:

Current Remeron labeling without carve-out:



ANDA Labeling with carve-out:

The above, the last paragraph in the Clinical Pharmacology section, will be carved out.

The **ADVERSE REACTIONS** and **PRECAUTIONS** sections of the package insert for generic mirtazapine will remain the same as that in the current Remeron labeling, except for the few references to the long-term study. In addition, the term "Major Depressive Disorder" has replaced .

The Division of Neuropharmacological Drug Products believes that generic Remeron (mirtazapine) applications can be approved without including the maintenance use of this drug product in major depressive disorder. Omitting the protected text, as indicated above, will not render the generic products less safe or effective than the listed drug for all remaining non-protected conditions of use.

**CENTER FOR DRUG
EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

76-119

CORRESPONDENCE



Administrative Offices:
TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

Phone: (215) 591 3141
FAX: (215) 591 8812

January 22, 2003

Gary Buehler, Director
Food and Drug Administration
Office of Generic Drugs
Document Control Room
Metro Park North II
7500 Standish Place, Room150
Rockville, MD 20855-2773

TELEPHONE AMENDMENT

~~ORIG~~ AMENDMENT

NIAF

ANDA 76-119
MIRTAZAPINE TABLETS 15 mg, 30 mg, and 45 mg
TELEPHONE AMENDMENT – RESPONSE TO JANUARY 21, 2003 TELEPHONE
REQUEST

Dear Mr. Buehler:

We submit herewith a telephone amendment to the above referenced pending ANDA in response to a telephone request made by Mark Anderson of your Office on January 21, 2003. Specifically, we are providing final printed insert labeling that includes reference to only the 15 mg and 30 mg tablet strengths. Enclosed please find 12 final printed copies of our revised insert labeling as well as a comparison of the newly revised labeling with that which was last submitted to this ANDA which demonstrates that the only change is the removal of the 45 mg product.

The enclosed final printed labeling is provided for your review and approval of the 15 mg and 30 mg tablet strengths of Mirtazapine Tablets as presented in ANDA 76-119. If you have any questions or comments please do not hesitate to contact me via telephone at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,

PE
Enclosure

RECEIVED
JAN 23 2003
OGD / CDER



Administrative Offices:
TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
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Philip Erickson, R.Ph.
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January 7, 2003

ORIG AMENDMENT

N/A

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

**MINOR AMENDMENT
FINAL APPROVAL REQUESTED**

ANDA #76-119
MIRTAZAPINE TABLETS, 15 mg, 30 mg, and 45 mg
MINOR AMENDMENT – FINAL APPROVAL REQUESTED

Dear Mr. Buehler:

We submit herewith a minor amendment to the above-referenced, tentatively approved, abbreviated new drug application in accord with a letter from the Office of Generic Drugs dated October 8, 2002 which granted tentative approval of this file. Please note, revised final print insert labeling was submitted on November 25, 2002 in response to your letter dated November 6, 2002. Additionally, TEVA Pharmaceuticals USA provided a copy of the December 18, 2002 court order in favor of TEVA, on December 19, 2002. At this time we also formally requested final approval of our pending ANDA. Beyond the information supplied in the aforementioned submissions, no substantive changes have been made to the control documentation submitted in this application.

This information is submitted for your review and final approval of ANDA # 76-119. Should there be any questions, please do not hesitate to contact me at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,

PE/cw
Enclosures

RECEIVED

JAN 08 2003

OGD / CDER

PEW
1-13-03



Administrative Offices:
 TEVA PHARMACEUTICALS USA
 1090 Horsham Road, PO Box 1090
 North Wales, PA 19454-1090

Philip Erickson, R.Ph.
 Director, Regulatory Affairs
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 FAX: (215) 591 8812

December 19, 2002

Gary Buehler, Director
 Office of Generic Drugs
 Food and Drug Administration
 Document Control Room
 Metro Park North II
 7500 Standish Place, Room 150
 Rockville, MD 20855-2773

**NOTICE OF COURT ORDER -
 COMMENCEMENT OF EXCLUSIVITY**

NEW CORRESP

NC

NAZ
 - Summary judgement
 granted for 1099.
 12/27/02
 P.M.P.

ANDA #76-119
 MIRTAZAPINE TABLETS, 15 mg, 30 mg, and 45 mg
 NOTICE OF COURT ORDER - COMMENCEMENT OF EXCLUSIVITY

Dear Mr. Buehler:

We submit herewith notification of a court order issued by the United States District Court, District of New Jersey regarding the Civil Action between the plaintiffs, Organon Inc. and Akzo Nobel N.V., and the defendants, Teva Pharmaceuticals, Inc. and Mylan Pharmaceuticals, Inc. This court order is dated December 18, 2002 and grants defendants' motion for summary judgement. As such, the 180 day exclusivity period to which Teva Pharmaceuticals USA is entitled as the first applicant to submit a substantially complete Abbreviated New Drug Application containing certification in accord with Section 505(j)(2)(A)(vii)(IV) of the Federal Food, Drug and Cosmetic Act, as amended, has commenced. Teva Pharmaceuticals USA provides a copy of the aforementioned court order herein and requests expeditious approval of our pending ANDA that had received tentative approval on October 8, 2002.

This information is submitted for your review and final approval of ANDA # 76-119. Should there be any questions, please do not hesitate to contact me at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,

PE/rsv
 Enclosures

RECEIVED
 DEC 20 2002
 OGD / CDER



Administrative Offices:

TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
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Philip Erickson, R.Ph.
Director, Regulatory Affairs
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November 25, 2002

Gary Buehler
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

LABELING AMENDMENT

ORIG AMENDMENT

N/AF

FPL

ANDA #76-119
MIRTAZAPINE TABLETS 15 mg, 30 mg and 45 mg
LABELING AMENDMENT – RESPONSE TO NOVEMBER 6, 2002 REVIEW LETTER

Dear Mr. Buehler:

We submit herewith a labeling amendment in response to a letter dated November 6, 2002 from the Labeling Review Branch. For ease of review, a copy of the review letter is included in **Attachment 1**. Specifically, the review letter requested changes to our proposed package insert in accord with recent changes in the reference listed drug's labeling approved April 9 and September 30, 2002. Enclosed, please find 12 final printed copies of our revised package insert (**Attachment 2**) and a comparison of our package insert with the current reference listed drug's package insert (**Attachment 3**).

The information provided herein represents, in our opinion, a complete response to your letter dated November 6, 2002 and is submitted towards the continued review and approval of the above referenced pending ANDA. If you have any questions, please do not hesitate to contact me at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,


PE/ac
Enclosures

RECEIVED

NOV 26 2002

OGD / CDER



301

Administrative Offices:
TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

Philip Erickson, R.Ph.
Director, Regulatory Affairs
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FAX: (215) 591 8812

ORIG AMENDMENT

N/AF

July 5, 2002

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

*Labeling review
drafted 7/12/02
A. Vega*

LABELING AMENDMENT

ANDA # 76-119
MIRTAZAPINE TABLETS, 15 mg, 30 mg and 45 mg
LABELING AMENDMENT – RESPONSE TO JULY 5, 2002 REVIEW LETTER

Dear Mr. Buehler:

We submit herewith a labeling amendment in response to a letter dated July 5, 2002 from the labeling review branch. For ease of review, please find a copy of the July 5, 2002 review letter in **Attachment 1**.

The package insert labeling has been revised as requested. Please find 12 final printed labels and a comparison of our proposed labeling with our last submission in **Attachment 2**.

This information is submitted for your continued review and approval of this pending ANDA. If there are any further questions, please do not hesitate to contact me at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,

PE/jb
Enclosures

RECEIVED

JUL 08 2002

OGD / ODER



Administrative Offices:
TEVA PHARMACEUTICALS USA
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July 3, 2002

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

PATENT AMENDMENT

NEW CORRESP
NC

NAT 7/5/02
P.M.P.

ANDA # 76-119
MIRTAZAPINE TABLETS, 15 mg, 30 mg, and 45 mg
PATENT AMENDMENT- PATENT CERTIFICATION FOR U.S. PATENT 6,399,310

Dear Mr. Buehler:

We submit herewith an amendment to the above-referenced pending ANDA for the purpose of providing an additional patent certification statement. Teva has recently become aware of the existence of U.S. Patent No. 6,399,310, which on its face, has been assigned to Organon. On information and belief that the aforementioned patent is sought to be listed in FDA's *Approved Drug Product with Therapeutic Equivalence Evaluations* for the reference listed drug Remeron[®] Tablets, Teva wishes to provide the enclosed certification with regard to this patent. Please note that U.S. Patent No. 6,399,310 issued on June 4, 2002. Therefore, Teva anticipates that Organon, as owner of NDA 20-415 for Remeron[®] Tablets, would take steps to list this patent within 30 days of issue so as not to be considered late listed.

Should you have any questions concerning the information contained herein, please do not hesitate to contact me at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,

PE/jbp
Enclosures

RECEIVED

JUL 05 2002

OGD / CDER



Administrative Offices:
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NEW CORRESP
NC

July 2, 2002

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

PATENT AMENDMENT

7/3/02
RAF P.M.P.

ANDA # 76-119
MIRTAZAPINE TABLETS, 15 mg, 30 mg, and 45 mg
PATENT AMENDMENT- PATENT CERTIFICATION FOR U.S. PATENT 6,399,310

Dear Mr. Buehler:

We submit herewith an amendment to the above-referenced pending ANDA for the purpose of providing an additional patent certification statement. Teva has recently become aware of the existence of U.S. Patent No. 6,399,310, which on its face, has been assigned to Organon. On information and belief that the aforementioned patent is sought to be listed in FDA's *Approved Drug Product with Therapeutic Equivalence Evaluations* for the reference listed drug Remeron[®] Tablets, Teva wishes to provide the enclosed certification with regard to this patent. Please note that U.S. Patent No. 6,399,310 issued on June 4, 2002. Therefore, Teva anticipates that Organon, as owner of NDA 20-415 for Remeron[®] Tablets, would take steps to list this patent within 30 days of issue so as not to be considered late listed.

Should you have any questions concerning the information contained herein, please do not hesitate to contact me at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,

PE/jbp
Enclosures

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JUL 03 2002

OGD / CDER



Administrative Offices:
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3.1

NEW CORRESP
NC

July 1, 2002

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

PATENT AMENDMENT

NAZ P.M.P.
- As of current Dockets
Page (June 21, 2002) and OB'
310 not listed yet.
8/3/02

ANDA # 76-119
MIRTAZAPINE TABLETS, 15 mg, 30 mg, and 45 mg
PATENT AMENDMENT- PATENT CERTIFICATION FOR U.S. PATENT 6,399,310

Dear Mr. Buehler:

We submit herewith an amendment to the above-referenced pending ANDA for the purpose of providing an additional patent certification statement. Teva has recently become aware of the existence of U.S. Patent No. 6,399,310, which on its face, has been assigned to Organon. On information and belief that the aforementioned patent is sought to be listed in FDA's *Approved Drug Product with Therapeutic Equivalence Evaluations* for the reference listed drug Remeron[®] Tablets, Teva wishes to provide the enclosed certification with regard to this patent. Please note that U.S. Patent No. 6,399,310 issued on June 4, 2002. Therefore, Teva anticipates that Organon, as owner of NDA 20-415 for Remeron[®] Tablets, would take steps to list this patent within 30 days of issue so as not to be considered late listed.

Should you have any questions concerning the information contained herein, please do not hesitate to contact me at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,

PE/jbp
Enclosures

RECEIVED
JUL 02 2002
OGD / CDER



Administrative Offices:
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3.1

June 28, 2002

NEW CORRESP

NC

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

PATENT AMENDMENT

7/2
NAT
- Not listed yet.
P.M.P

ANDA # 76-119
MIRTAZAPINE TABLETS, 15 mg, 30 mg, and 45 mg
PATENT AMENDMENT- PATENT CERTIFICATION FOR U.S. PATENT 6,399,310

Dear Mr. Buehler:

We submit herewith an amendment to the above-referenced pending ANDA for the purpose of providing an additional patent certification statement. Teva has recently become aware of the existence of U.S. Patent No. 6,399,310, which on its face, has been assigned to Organon. On information and belief that the aforementioned patent is sought to be listed in FDA's *Approved Drug Product with Therapeutic Equivalence Evaluations* for the reference listed drug Remeron[®] Tablets, Teva wishes to provide the enclosed certification with regard to this patent. Please note that U.S. Patent No. 6,399,310 issued on June 4, 2002. Therefore, Teva anticipates that Organon, as owner of NDA 20-415 for Remeron[®] Tablets, would take steps to list this patent within 30 days of issue so as not to be considered late listed.

Should you have any questions concerning the information contained herein, please do not hesitate to contact me at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,

Philip Erickson / DJ
PE/jbp
Enclosures

RECEIVED

JUL 01 2002

OGD / CDER



Administrative Offices:
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June 27, 2002

NEW CORRESP

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

PATENT AMENDMENT

Not 6/29/02
Not listed yet
P.M.P

ANDA # 76-119
MIRTAZAPINE TABLETS, 15 mg, 30 mg, and 45 mg
PATENT AMENDMENT- PATENT CERTIFICATION FOR U.S. PATENT 6,399,310

Dear Mr. Buehler:

We submit herewith an amendment to the above-referenced pending ANDA for the purpose of providing an additional patent certification statement. Teva has recently become aware of the existence of U.S. Patent No. 6,399,310, which on its face, has been assigned to Organon. On information and belief that the aforementioned patent is sought to be listed in FDA's *Approved Drug Product with Therapeutic Equivalence Evaluations* for the reference listed drug Remeron[®] Tablets, Teva wishes to provide the enclosed certification with regard to this patent. Please note that U.S. Patent No. 6,399,310 issued on June 4, 2002. Therefore, Teva anticipates that Organon, as owner of NDA 20-415 for Remeron[®] Tablets, would take steps to list this patent within 30 days of issue so as not to be considered late listed.

Should you have any questions concerning the information contained herein, please do not hesitate to contact me at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,

Philip Erickson 102
PE/jbp
Enclosures

RECEIVED

JUN 28 2002

OGD / CDER



Administrative Offices:
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June 26, 2002

NEW CORRESP
NC

PATENT AMENDMENT

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

NBI 6/28
Not listed yet
P.M.P

ANDA # 76-119
MIRTAZAPINE TABLETS, 15 mg, 30 mg, and 45 mg
PATENT AMENDMENT- PATENT CERTIFICATION FOR U.S. PATENT 6,399,310

Dear Mr. Buehler:

We submit herewith an amendment to the above-referenced pending ANDA for the purpose of providing an additional patent certification statement. Teva has recently become aware of the existence of U.S. Patent No. 6,399,310, which on its face, has been assigned to Organon. On information and belief that the aforementioned patent is sought to be listed in FDA's *Approved Drug Product with Therapeutic Equivalence Evaluations* for the reference listed drug Remeron[®] Tablets, Teva wishes to provide the enclosed certification with regard to this patent. Please note that U.S. Patent No. 6,399,310 issued on June 4, 2002. Therefore, Teva anticipates that Organon, as owner of NDA 20-415 for Remeron[®] Tablets, would take steps to list this patent within 30 days of issue so as not to be considered late listed.

Should you have any questions concerning the information contained herein, please do not hesitate to contact me at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,

Philip Erickson / DG
PE/jbp
Enclosures

RECEIVED

JUN 27 2002

OGD / CDER



Administrative Offices:
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1090 Horsham Road, PO Box 1090
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Philip Erickson, R.Ph.
Director, Regulatory Affairs
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FAX: (215) 591 8600

NEW CORRESP
NC

June 25, 2002

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

PATENT AMENDMENT

6/27 NAF
Not listed yet
P.M.P

ANDA # 76-119
MIRTAZAPINE TABLETS, 15 mg, 30 mg, and 45 mg
PATENT AMENDMENT- PATENT CERTIFICATION FOR U.S. PATENT 6,399,310

Dear Mr. Buehler:

We submit herewith an amendment to the above-referenced pending ANDA for the purpose of providing an additional patent certification statement. Teva has recently become aware of the existence of U.S. Patent No. 6,399,310, which on its face, has been assigned to Organon. On information and belief that the aforementioned patent is sought to be listed in FDA's *Approved Drug Product with Therapeutic Equivalence Evaluations* for the reference listed drug Remeron[®] Tablets, Teva wishes to provide the enclosed certification with regard to this patent. Please note that U.S. Patent No. 6,399,310 issued on June 4, 2002. Therefore, Teva anticipates that Organon, as owner of NDA 20-415 for Remeron[®] Tablets, would take steps to list this patent within 30 days of issue so as not to be considered late listed.

Should you have any questions concerning the information contained herein, please do not hesitate to contact me at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,

Philip Erickson / DSG
PE/jbp
Enclosures

RECEIVED
JUN 26 2002
OGD / CDER



Administrative Offices:
 TEVA PHARMACEUTICALS USA
 1090 Horsham Road, PO Box 1090
 North Wales, PA 19454-1090

Philip Erickson, R.Ph.
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Phone: (215) 591 3000
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NC

June 24, 2002

Gary Buehler, Director
 Office of Generic Drugs
 Food and Drug Administration
 Document Control Room
 Metro Park North II
 7500 Standish Place, Room 150
 Rockville, MD 20855-2773

PATENT AMENDMENT

W&Z 6/26
Not listed yet
P.M.P

ANDA # 76-119
 MIRTAZAPINE TABLETS, 15 mg, 30 mg, and 45 mg
 PATENT AMENDMENT- PATENT CERTIFICATION FOR U.S. PATENT 6,399,310

Dear Mr. Buehler:

We submit herewith an amendment to the above-referenced pending ANDA for the purpose of providing an additional patent certification statement. Teva has recently become aware of the existence of U.S. Patent No. 6,399,310, which on its face, has been assigned to Organon. On information and belief that the aforementioned patent is sought to be listed in FDA's *Approved Drug Product with Therapeutic Equivalence Evaluations* for the reference listed drug Remeron[®] Tablets, Teva wishes to provide the enclosed certification with regard to this patent. Please note that U.S. Patent No. 6,399,310 issued on June 4, 2002. Therefore, Teva anticipates that Organon, as owner of NDA 20-415 for Remeron[®] Tablets, would take steps to list this patent within 30 days of issue so as not to be considered late listed.

Should you have any questions concerning the information contained herein, please do not hesitate to contact me at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,

Philip Erickson
 PE/jbp
 Enclosures

RECEIVED

JUN 25 2002

OGD / CDER



Administrative Offices:
 TEVA PHARMACEUTICALS USA
 1090 Horsham Road, PO Box 1090
 North Wales, PA 19454-1090

Philip Erickson, R.Ph.
 Director, Regulatory Affairs
 Solid Oral Dosage Forms

Phone: (215) 591 3000
 FAX: (215) 591 8600

NEW CORRESP
 NC

June 21, 2002

Gary Buehler, Director
 Office of Generic Drugs
 Food and Drug Administration
 Document Control Room
 Metro Park North II
 7500 Standish Place, Room 150
 Rockville, MD 20855-2773

PATENT AMENDMENT

NAI
 6/25 Not listed yet.
 P.M.P.

ANDA # 76-119
 MIRTAZAPINE TABLETS, 15 mg, 30 mg, and 45 mg
 PATENT AMENDMENT- PATENT CERTIFICATION FOR U.S. PATENT 6,399,310

Dear Mr. Buehler:

We submit herewith an amendment to the above-referenced pending ANDA for the purpose of providing an additional patent certification statement. Teva has recently become aware of the existence of U.S. Patent No. 6,399,310, which on its face, has been assigned to Organon. On information and belief that the aforementioned patent is sought to be listed in FDA's *Approved Drug Product with Therapeutic Equivalence Evaluations* for the reference listed drug Remeron[®] Tablets, Teva wishes to provide the enclosed certification with regard to this patent. Please note that U.S. Patent No. 6,399,310 issued on June 4, 2002. Therefore, Teva anticipates that Organon, as owner of NDA 20-415 for Remeron[®] Tablets, would take steps to list this patent within 30 days of issue so as not to be considered late listed.

Should you have any questions concerning the information contained herein, please do not hesitate to contact me at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,



PE/jbp
 Enclosures

RECEIVED

JUN 24 2002

OGD / CDER



Administrative Offices:
TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

Phone: (215) 591 3000
FAX: (215) 591 8600

NKI
noted 7-1-02
Patent not yet listed in OIB
According to docket 955-017
not updated 6-21-02 ... this
cert is invalid
NEW CORRES:
NC

June 20, 2002

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

PATENT AMENDMENT

ANDA # 76-119
MIRTAZAPINE TABLETS, 15 mg, 30 mg, and 45 mg
PATENT AMENDMENT- PATENT CERTIFICATION FOR U.S. PATENT 6,399,310

Dear Mr. Buehler:

We submit herewith an amendment to the above-referenced pending ANDA for the purpose of providing an additional patent certification statement. Teva has recently become aware of the existence of U.S. Patent No. 6,399,310, which on its face, has been assigned to Organon. On information and belief that the aforementioned patent is sought to be listed in FDA's *Approved Drug Product with Therapeutic Equivalence Evaluations* for the reference listed drug Remeron[®] Tablets, Teva wishes to provide the enclosed certification with regard to this patent. Please note that U.S. Patent No. 6,399,310 issued on June 4, 2002. Therefore, Teva anticipates that Organon, as owner of NDA 20-415 for Remeron[®] Tablets, would take steps to list this patent within 30 days of issue so as not to be considered late listed.

Should you have any questions concerning the information contained herein, please do not hesitate to contact me at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,

PE/jbp
Enclosures

RECEIVED

JUN 21 2002

OGD / CDER



3!

Administrative Offices:
TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

Phone: (215) 591 3000
FAX: (215) 591 8600

June 19, 2002

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

NEW CORRESP

Handwritten notes:
NMT NC
MUS 7-1-02
Patent not yet listed in O.B. Acaolins
to Docket 955-017 first year 6-21-02
∴ this cert is ~~not~~ wanted

PATENT AMENDMENT

ANDA # 76-119

MIRTAZAPINE TABLETS, 15 mg, 30 mg, and 45 mg
PATENT AMENDMENT- PATENT CERTIFICATION FOR U.S. PATENT 6,399,310

Dear Mr. Buehler:

We submit herewith an amendment to the above-referenced pending ANDA for the purpose of providing an additional patent certification statement. Teva has recently become aware of the existence of U.S. Patent No. 6,399,310, which on its face, has been assigned to Organon. On information and belief that the aforementioned patent is sought to be listed in FDA's *Approved Drug Product with Therapeutic Equivalence Evaluations* for the reference listed drug Remeron[®] Tablets, Teva wishes to provide the enclosed certification with regard to this patent. Please note that U.S. Patent No. 6,399,310 issued on June 4, 2002. Therefore, Teva anticipates that Organon, as owner of NDA 20-415 for Remeron[®] Tablets, would take steps to list this patent within 30 days of issue so as not to be considered late listed.

Should you have any questions concerning the information contained herein, please do not hesitate to contact me at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,

Philip Erickson
PE/jbp
Enclosures

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JUN 20 2002
OGD / CDER



Administrative Offices:
 TEVA PHARMACEUTICALS USA
 1090 Horsham Road, PO Box 1090
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 Director, Regulatory Affairs
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 FAX: (215) 591 8600

NEW CORRESP

June 18, 2002

Gary Buehler, Director
 Office of Generic Drugs
 Food and Drug Administration
 Document Control Room
 Metro Park North II
 7500 Standish Place, Room 150
 Rockville, MD 20855-2773

NAT NC
Patent not yet listed in O.D. According to Deck of 955-0117 listed updated 6/14/02
∴ this cert is correct.

PATENT AMENDMENT

ANDA # 76-119
 MIRTAZAPINE TABLETS, 15 mg, 30 mg, and 45 mg
 PATENT AMENDMENT- PATENT CERTIFICATION FOR U.S. PATENT 6,399,310

Dear Mr. Buehler:

We submit herewith an amendment to the above-referenced pending ANDA for the purpose of providing an additional patent certification statement. Teva has recently become aware of the existence of U.S. Patent No. 6,399,310, which on its face, has been assigned to Organon. On information and belief that the aforementioned patent is sought to be listed in FDA's *Approved Drug Product with Therapeutic Equivalence Evaluations* for the reference listed drug Remeron[®] Tablets, Teva wishes to provide the enclosed certification with regard to this patent. Please note that U.S. Patent No. 6,399,310 issued on June 4, 2002. Therefore, Teva anticipates that Organon, as owner of NDA 20-415 for Remeron[®] Tablets, would take steps to list this patent within 30 days of issue so as not to be considered late listed.

Should you have any questions concerning the information contained herein, please do not hesitate to contact me at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,



PE/jbp
 Enclosures

RECEIVED
 JUN 19 2002
 OGD / CDER



Administrative Offices:
 TEVA PHARMACEUTICALS USA
 1090 Horsham Road, PO Box 1090
 North Wales, PA 19454-1090

Philip Erickson, R.Ph.
 Director, Regulatory Affairs
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 FAX: (215) 591 8600

June 14, 2002

Gary Buehler, Director
 Office of Generic Drugs
 Food and Drug Administration
 Document Control Room
 Metro Park North II
 7500 Standish Place, Room 150
 Rockville, MD 20855-2773

NEW CORRESP
PATENT AMENDMENT
 MKT
 NC
 PATENT NOT YET LISTED IN O.B.
 According to check 955-0117 last updated
 6-21-02 :: this cert is mounted

ANDA # 76-119
 MIRTAZAPINE TABLETS, 15 mg, 30 mg, and 45 mg
 PATENT AMENDMENT- PATENT CERTIFICATION FOR U.S. PATENT 6,399,310

Dear Mr. Buehler:

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Should you have any questions concerning the information contained herein, please do not hesitate to contact me at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,

PE/jbp
 Enclosures

RECEIVED
 JUN 18 2002
 OGD / CDER



Administrative Offices:
 TEVA PHARMACEUTICALS USA
 1090 Horsham Road, PO Box 1090
 North Wales, PA 19454-1090

Philip Erickson, R.Ph.
 Director, Regulatory Affairs
 Solid Oral Dosage Forms

Phone: (215) 591 3000
 FAX: (215) 591 8600

NAT
MMS 7-1-02
Patent not yet listed in O.B.
According to Docket 95-017 list
updated to 2002. ∴ this cert
is wrong

June 13, 2002

Gary Buehler, Director
 Office of Generic Drugs
 Food and Drug Administration
 Document Control Room
 Metro Park North II
 7500 Standish Place, Room 150
 Rockville, MD 20855-2773

PATENT AMENDMENT

NEW CORRESP
 NC

ANDA # 76-119
 MIRTAZAPINE TABLETS, 15 mg, 30 mg, and 45 mg
 PATENT AMENDMENT- PATENT CERTIFICATION FOR U.S. PATENT 6,399,310

Dear Mr. Buehler:

We submit herewith an amendment to the above-referenced pending ANDA for the purpose of providing an additional patent certification statement. Teva has recently become aware of the existence of U.S. Patent No. 6,399,310, which on its face, has been assigned to Organon. On information and belief that the aforementioned patent is sought to be listed in FDA's *Approved Drug Product with Therapeutic Equivalence Evaluations* for the reference listed drug Remeron[®] Tablets, Teva wishes to provide the enclosed certification with regard to this patent. Please note that U.S. Patent No. 6,399,310 issued on June 4, 2002. Therefore, Teva anticipates that Organon, as owner of NDA 20-415 for Remeron[®] Tablets, would take steps to list this patent within 30 days of issue so as not to be considered late listed.

Should you have any questions concerning the information contained herein, please do not hesitate to contact me at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,

PE/jbp
 Enclosures

RECEIVED
 JUN 14 2002
 OGD / CDER



Administrative Offices:
TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

Phone: (215) 591 3000
FAX: (215) 591 8600

NAC
WMS 6-19-02
Patent not yet posted in ORB
According to Docket 955-017
this cert is correct

updated 6-14-02

June 12, 2002

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

PATENT AMENDMENT

NEW CORRESP
NC

ANDA # 76-119
MIRTAZAPINE TABLETS, 15 mg, 30 mg, and 45 mg
PATENT AMENDMENT- PATENT CERTIFICATION FOR U.S. PATENT 6,399,310

Dear Mr. Buehler:

We submit herewith an amendment to the above-referenced pending ANDA for the purpose of providing an additional patent certification statement. Teva has recently become aware of the existence of U.S. Patent No. 6,399,310, which on its face, has been assigned to Organon. On information and belief that the aforementioned patent is sought to be listed in FDA's *Approved Drug Product with Therapeutic Equivalence Evaluations* for the reference listed drug Remeron[®] Tablets, Teva wishes to provide the enclosed certification with regard to this patent. Please note that U.S. Patent No. 6,399,310 issued on June 4, 2002. Therefore, Teva anticipates that Organon, as owner of NDA 20-415 for Remeron[®] Tablets, would take steps to list this patent within 30 days of issue so as not to be considered late listed.

Should you have any questions concerning the information contained herein, please do not hesitate to contact me at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,

PE/jbp
Enclosures

RECEIVED

JUN 13 2002

OGD / CDER



Administrative Offices:
 TEVA PHARMACEUTICALS USA
 1090 Horsham Road, PO Box 1090
 North Wales, PA 19454-1090

Philip Erickson, R.Ph.
 Director, Regulatory Affairs
 Solid Oral Dosage Forms

Phone: (215) 591 3000
 FAX: (215) 591 8600

updated 6-14-02

~~NAZ~~
 MTS 6-19-02
 Patent not yet tested in O.B.
 According to Dept of 955-0117
 this cert is required

June 11, 2002

Gary Buehler, Director
 Office of Generic Drugs
 Food and Drug Administration
 Document Control Room
 Metro Park North II
 7500 Standish Place, Room 150
 Rockville, MD 20855-2773

PATENT AMENDMENT

ANDA # 76-119
 MIRTAZAPINE TABLETS, 15 mg, 30 mg, and 45 mg
 PATENT AMENDMENT- PATENT CERTIFICATION FOR U.S. PATENT 6,399,310

Dear Mr. Buehler:

We submit herewith an amendment to the above-referenced pending ANDA for the purpose of providing an additional patent certification statement. Teva has recently become aware of the existence of U.S. Patent No. 6,399,310, which on its face, has been assigned to Organon. On information and belief that the aforementioned patent is sought to be listed in FDA's *Approved Drug Product with Therapeutic Equivalence Evaluations* for the reference listed drug Remeron[®] Tablets, Teva wishes to provide the enclosed certification with regard to this patent. Please note that U.S. Patent No. 6,399,310 issued on June 4, 2002. Therefore, Teva anticipates that Organon, as owner of NDA 20-415 for Remeron[®] Tablets, would take steps to list this patent within 30 days of issue so as not to be considered late listed.

Should you have any questions concerning the information contained herein, please do not hesitate to contact me at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,

PE/jbp
 Enclosures

RECEIVED

JUN 12 2002

OGD / CDER



Administrative Offices:
TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

Phone: (215) 591 3000
FAX: (215) 591 8600

updated 6/14/02
NOTE
Patent not yet listed in ORB
according to Docket 955-0117
Therefore this cert is invalid
NEW CORRESP
NC

June 10, 2002

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

PATENT AMENDMENT

ANDA # 76-119
MIRTAZAPINE TABLETS, 15 mg, 30 mg, and 45 mg
PATENT AMENDMENT- PATENT CERTIFICATION FOR U.S. PATENT 6,399,310

Dear Mr. Buehler:

We submit herewith an amendment to the above-referenced pending ANDA for the purpose of providing an additional patent certification statement. Teva has recently become aware of the existence of U.S. Patent No. 6,399,310, which on its face, has been assigned to Organon. On information and belief that the aforementioned patent is sought to be listed in FDA's *Approved Drug Product with Therapeutic Equivalence Evaluations* for the reference listed drug Remeron[®] Tablets, Teva wishes to provide the enclosed certification with regard to this patent. Please note that U.S. Patent No. 6,399,310 issued on June 4, 2002. Therefore, Teva anticipates that Organon, as owner of NDA 20-415 for Remeron[®] Tablets, would take steps to list this patent within 30 days of issue so as not to be considered late listed.

Should you have any questions concerning the information contained herein, please do not hesitate to contact me at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,


PE/jbp
Enclosures

RECEIVED
JUN 11 2002
OGD / CDER



Administrative Offices:
 TEVA PHARMACEUTICALS USA
 1090 Horsham Road, PO Box 1090
 North Wales, PA 19454-1090

Phone: (215) 591 3000
 FAX: (215) 591 8600

reopened 6-14-02

Philip Erickson, R.Ph.
 Director, Regulatory Affairs
 Solid Oral Dosage Forms

*NET
 NTS 6-19-02
 Patent not yet listed in ORB.
 According to Deckel 955-017
 this cert is invalid
 NEW CORRESP
 NC*

June 7, 2002

Gary Buehler, Director
 Office of Generic Drugs
 Food and Drug Administration
 Document Control Room
 Metro Park North II
 7500 Standish Place, Room 150
 Rockville, MD 20855-2773

PATENT AMENDMENT

ANDA # 76-119
 MIRTAZAPINE TABLETS, 15 mg, 30 mg, and 45 mg
 PATENT AMENDMENT- PATENT CERTIFICATION FOR U.S. PATENT 6,399,310

Dear Mr. Buehler:

We submit herewith an amendment to the above-referenced pending ANDA for the purpose of providing an additional patent certification statement. Teva has recently become aware of the existence of U.S. Patent No. 6,399,310, which on its face, has been assigned to Organon. On information and belief that the aforementioned patent is sought to be listed in FDA's *Approved Drug Product with Therapeutic Equivalence Evaluations* for the reference listed drug Remeron[®] Tablets, Teva wishes to provide the enclosed certification with regard to this patent. Please note that U.S. Patent No. 6,399,310 issued on June 4, 2002. Therefore, Teva anticipates that Organon, as owner of NDA 20-415 for Remeron[®] Tablets, would take steps to list this patent within 30 days of issue so as not to be considered late listed.

Should you have any questions concerning the information contained herein, please do not hesitate to contact me at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,

Philip Erickson

PE/jbp
 Enclosures

RECEIVED

JUN 10 2002

OGD / CDER



Administrative Offices:

TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

Phone: (215) 591 3000
FAX: (215) 591 8600

June 6, 2002

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

NAI 6/p/ok
Not listed in
OB' yet.
P.M.P

PATENT AMENDMENT

NEW CORRESP

NC

ANDA # 76-119
MIRTAZAPINE TABLETS, 15 mg, 30 mg, and 45 mg
PATENT AMENDMENT- PATENT CERTIFICATION FOR U.S. PATENT 6,399,310

Dear Mr. Buehler:

We submit herewith an amendment to the above-referenced pending ANDA for the purpose of providing an additional patent certification statement. Teva has recently become aware of the existence of U.S. Patent No. 6,399,310, which on its face, has been assigned to Organon. On information and belief that the aforementioned patent is sought to be listed in FDA's *Approved Drug Product with Therapeutic Equivalence Evaluations* for the reference listed drug Remeron[®] Tablets, Teva wishes to provide the enclosed certification with regard to this patent. Please note that U.S. Patent No. 6,399,310 issued on June 4, 2002. Therefore, Teva anticipates that Organon, as owner of NDA 20-415 for Remeron[®] Tablets, would take steps to list this patent within 30 days of issue so as not to be considered late listed.

Should you have any questions concerning the information contained herein, please do not hesitate to contact me at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,

PE/jbp
Enclosures

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JUN 06 2002

OGD / CDER



Administrative Offices:
TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

Deborah A. Jaskot, M.S., RAC
Executive Director, Regulatory Affairs

Phone: (215) 591 3000
FAX: (215) 591 8600

May 20, 2002

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ANDA # 76-119
MIRTAZAPINE
UNSOLICITED AMENDMENT - LABELING

Dear Mr. Buehler:

Teva USA herein submits final printed insert labeling which has been revised from the labeling submitted in our amendment of May 1, 2002. The revision, undertaken after we received information from your Office that our last version did not represent a suitable carve out for the M-18 exclusivity, is minor and is highlighted in the attached side by side comparison to the previous version.

Teva fully believes that the attached final printed insert labeling represents an appropriate carve out of information covered by exclusivity and that it is complete for the duration of therapy proposed in our labeling. It is our understanding that with this labeling and a favorable decision of the district court in our motion for summary judgment (anticipated any day) that our application is eligible for final approval. On information and belief, Teva is eligible for 180 days exclusivity with the decision of the district court starting the clock. We therefore anticipate that the agency will expeditiously grant final effective approval as soon as evidence of a favorable court decision is provided as an amendment to this application.

Should you have any comments or questions, please feel free to contact me at (215) 591-3142 or via facsimile at (215) 591-8812.

Sincerely,

Deborah Jaskot

DAJ
Enclosures

N/AF
ORIG AMENDMENT

UNSOLICITED AMENDMENT
LABELING

FPL

RECEIVED
MAY 21 2002
OGD / CDER



Administrative Offices:

TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

Deborah A. Jaskot, M.S., RAC
Executive Director, Regulatory Affairs

Phone: (215) 591 3000
FAX: (215) 591 8600

May 1, 2002

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

**LABELING AMENDMENT
AND EXCLUSIVITY STATEMENT**

ORIG AMENDMENT
N/AF

ANDA #76-119
MIRTAZAPINE TABLETS, 15 mg, 30 mg, AND 45 mg
LABELING AMENDMENT AND EXCLUSIVITY STATEMENT

Dear Mr. Buehler:

Teva Pharmaceuticals USA is aware of an exclusivity granted to Organon, Inc., the sponsor of the reference listed drug, Remeron®, in conjunction with the approval of a supplement to the NDA for "the use of Remeron (mirtazapine) tablets in maintaining a response in patients with major depressive disorder." (See copy of supplemental NDA approval letter to NDA 20-415 enclosed.) We have reviewed the revised insert labeling approved with this supplemental NDA and have revised our own insert labeling in accord with this revision, excluding information dealing with maintenance dosing.

Twelve final printed copies of our revised insert as well as a side-by-side comparison to the previous version are enclosed for your review and approval. We request that this revised labeling be reviewed promptly as Teva anticipates a favorable ruling on our motion for summary judgment which will be heard on Friday, May 3. We believe our ANDA will be eligible for final approval upon the issuance of a favorable ruling and it is hoped that labeling revisions will not delay the granting of that final approval.

Additionally we have enclosed an exclusivity statement addressing the M-18 exclusivity granted to Organon, Inc.

Should there be any questions, please do not hesitate to contact me at (215) 591-3142 or via facsimile at (215) 591-8812.

Sincerely,

Deborah Jaskot

DJ
Enclosures

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MAY 02 2002

OGD / CDER

4. The formula for calculation of total impurities of the drug substance can be found in **Attachment 2**, 2485-IH, Ed. 006. The R & D method for the drug product Assay, Impurities & Degradation Products Determination (SI-11379, Ed. 03) as well as the Finished Product Procedure Manual (PR-0122, Ed. 03) for release and stability studies both contain the formula for the calculation of total impurities. Both of these procedure manuals are provided in **Attachment 4**.
5. The ~~size~~ size used in the Dissolution test is ~~_____~~ ~~_____~~. The dissolution test method has been revised to indicate the use of this ~~_____~~ in the ~~_____~~. This revised method, SI-17073, Ed. 02, is provided in **Attachment 5**.

Regarding the additional comment from Susan Zuk, we have confirmed that the change affecting the drug substance assay specification made by the supplier has been provided to their DMF. Evidence of this wider specification is provided in **Attachment 2**, the API manufacturer's raw material procedure manual.

This information is submitted for your continued review and approval of this pending application. If you have any questions, please do not hesitate to contact me at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,



PE/sah
Enclosures



Administrative Offices:
 TEVA PHARMACEUTICALS USA
 1090 Horsham Road, PO Box 1090
 North Wales, PA 19454-1090

Philip Erickson, R.Ph.
 Director, Regulatory Affairs
 Solid Oral Dosage Forms

Phone: (215) 591 3000
 FAX: (215) 591 8600

April 5, 2002

Gary Buehler, Director
 Office of Generic Drugs
 Food and Drug Administration
 Document Control Room
 Metro Park North II
 7500 Standish Place, Room 150
 Rockville, MD 20855-2773

**MINOR AMENDMENT
 90-DAY AMENDMENT**

ORIG AMENDMENT

N/Am

ANDA #76-119
 MIRTAZAPINE TABLETS, 15 mg, 30 mg, and 45 mg
 MINOR AMENDMENT - 90-DAY AMENDMENT

Dear Mr. Buehler:

We submit herewith a minor amendment to the above-referenced, tentatively approved, abbreviated new drug application in accord with a letter from the Office of Generic Drugs dated January 15, 2002 which granted tentative approval of this file. Please note that Teva has recently filed a motion for Summary Judgement with the court and anticipates a decision as early as April 2002. We believe the outcome of this Summary Judgement will make our application eligible for final approval.

Please note that the following documents have been revised since they were last submitted to the Agency in ANDA #76-119 or amendments to the file:

RECEIVED

Chemistry, Manufacturing and Controls:

APR 08 2002

OGD / CDER

Raw Material	Last Submitted Method	Current Method	Summary of Changes
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MPW
 4/9/02

Raw Material	Last Submitted Method	Current Method	Summary of Changes
[Redacted Content]			
		Attachment 8	25/NF 20.

Currently available room temperature stability data are provided in **Attachment 9**.

Provided in **Attachment 10** is a copy of the cover letter sent by the holder of DMF # _____ to the Agency dated March 12, 2002 updating their file.

This information is submitted for your review and final approval of ANDA # 76-119 upon resolution of court proceedings. Teva Pharmaceuticals USA commits to provide evidence of the court ruling in an amendment to this application once it is available. Should there be any questions, please do not hesitate to contact me at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,



PE/sah
Enclosures



Administrative Offices:
TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

Phone: (215) 591 3000
FAX: (215) 591 8600

December 28, 2001

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

NAM
ORIG AMENDMENT
TELEPHONE AMENDMENT

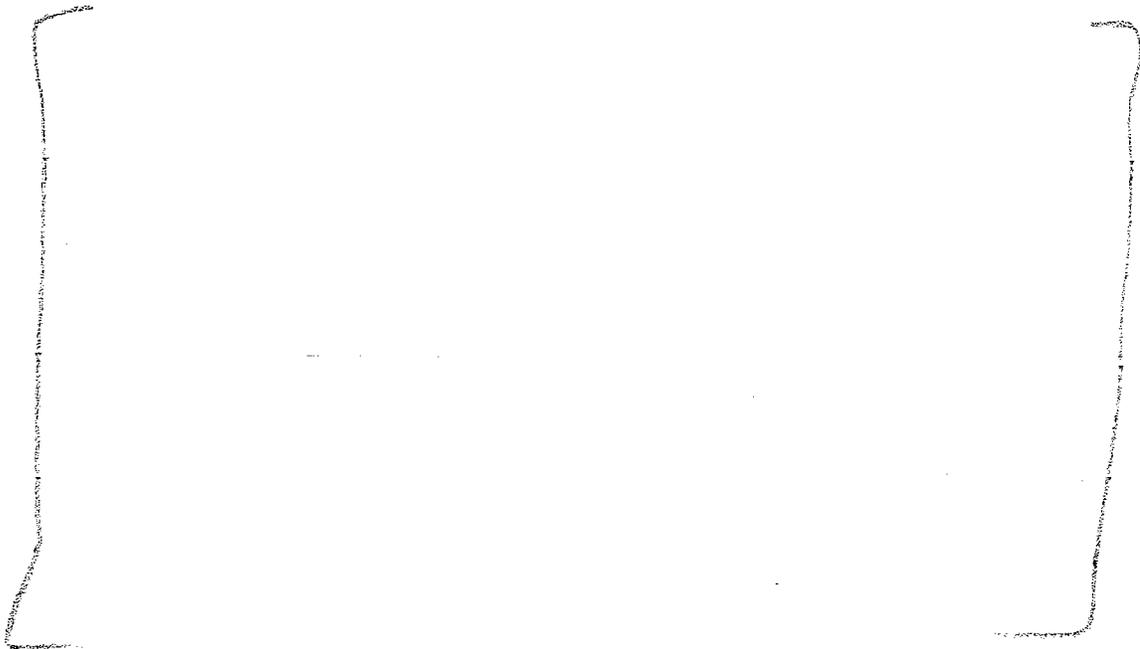
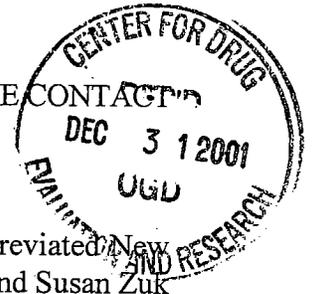
ANDA # 76-119

MIRTAZAPINE TABLETS, 15 mg, 30 mg and 45 mg

TELEPHONE AMENDMENT - RESPONSE TO DECEMBER 21, 2001 TELEPHONE CONTACT

Dear Mr. Buehler:

We submit herewith a telephone amendment to the above-referenced, pending Abbreviated New Drug Application in response to a telephone conversation between Mark Anderson and Susan Zuk of the Office of Generic Drugs and Philip Erickson, Director of Regulatory Affairs on December 21, 2001. Specifically, Mr. Anderson and Ms. Zuk requested that we provide data on the melting point of Mirtazapine drug substance and justify our content specification. These items are discussed in further detail below in the order in which they were presented in the afore mentioned conversation.



ANDA # 76-119

MIRTAZAPINE TABLETS, 15 mg, 30 mg and 45 mg

TELEPHONE AMENDMENT - RESPONSE TO DECEMBER 21, 2001 TELEPHONE CONTACT

PAGE 2 of 2

This information is submitted for your continued review and approval of this pending application. If you have any questions, please do not hesitate to contact me at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,

A handwritten signature in black ink, appearing to read "Paul E. Erbe", followed by a horizontal line extending to the right.

PE/jws

Enclosures



Administrative Offices:
TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

*NEW
MKS
12-07-01*

Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

Phone: (215) 591 3000
FAX: (215) 591 8600

NEW CORRESP
NC

December 4, 2001

AMENDMENT WITHDRAWAL

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ANDA #76-119
MIRTAZAPINE TABLETS, 15 mg, 30 mg, and 45 mg
REQUEST FOR WITHDRAWAL OF AMENDMENT DATED 11/14/01

Dear Mr. Buehler:

In response to a November 21, 2001 telephone conversation between Martin Shimer of the Office of Generic Drugs Regulatory Support Branch and Philip Erickson of TEVA Pharmaceuticals USA, we submit herewith a request to withdraw our patent amendment dated November 14, 2001. TEVA submitted the November 14, 2001 amendment towards the above-referenced pending ANDA for the purpose of providing patent certification for U.S. Patent No.6,303,595 (hereafter, "the '595 patent").

TEVA filed that certification on information and belief that the aforementioned patent was sought to be listed in FDA's *Approved Drug Product with Therapeutic Equivalence Evaluations*. However, we have been informed that FDA had not received a request for listing from the NDA holder regarding this patent within 30 days of its issue. Per Mr. Shimer's request, we respectfully request withdrawal of our November 14, 2001 Paragraph IV patent certification for the '595 patent.

Should you have any further comments or questions please do not hesitate to contact me via telephone at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,

Philip Erickson
PE/jbp





Corporate Headquarters:
TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

Phone: (215) 591 3000
FAX: (215) 591 8600

November 27, 2001

N/AF
ORIG AMENDMENT

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

UNSOLICITED AMENDMENT

ANDA #76-119
MIRTAZAPINE TABLETS, 15 mg, 30 mg, and 45 mg
UNSOLICITED AMENDMENT – FINAL PRINTED LABELING

Dear Mr. Buehler:

We submit herewith an unsolicited amendment to the above-referenced pending ANDA. Specifically we are submitting final printed labeling which is identical to the previously submitted labeling with the exception of corrections to minor typographical errors. The modifications are highlighted for ease of review.

We look forward to your continued review and approval of ANDA # 76-119. Should there be any questions, please do not hesitate to contact me at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,

PE/asg
Enclosures





Administrative Offices:
TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

Phone: (215) 591 3000
FAX: (215) 591 8600

NAT / MMS 11-21-01

NC

November 14, 2001

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

PATENT AMENDMENT

ANDA #76-119
MIRTAZAPINE TABLETS, 15 mg, 30 mg, and 45 mg
PATENT AMENDMENT -CERTIFICATION TO U.S. PATENT # 6,303,595

Dear Mr. Buehler:

We submit herewith an amendment to the above referenced pending ANDA for the purpose of providing an additional patent certification statement. Teva has recently become aware of the existence of U.S. Patent No.6,303,595 which, on its face, has been assigned to Akzo Nobel N.V. On information and belief that the aforementioned patent is sought to be listed in FDA's *Approved Drug Product with Therapeutic Equivalence Evaluations*, Teva wishes to provide the enclosed certification with regards to this patent.

Should you have any further comments or questions please do not hesitate to contact me via telephone at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,

PE/rsv
Enclosures





Administrative Offices:
TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

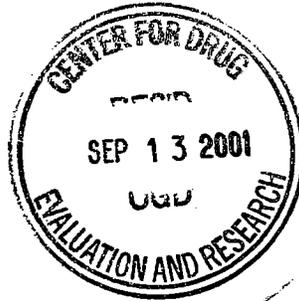
Phone: (215) 591 3000
FAX: (215) 591 8600

*Labeling remain
drafted 9/19/01
A. Vezza*

ORIG AMENDMENT
N/AM.

September 10, 2001

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773



MINOR AMENDMENT

ANDA #76-119
MIRTAZAPINE TABLETS, 15 mg, 30 mg, and 45 mg
MINOR AMENDMENT - RESPONSE TO JULY 20, 2001 REVIEW LETTER

Dear Mr. Buehler:

We submit herewith a minor amendment to the above-referenced pending abbreviated new drug application in response to a July 20, 2001 review letter from the Agency as well as an August 2, 2001 telephone conversation between Mark Anderson of the Office of Generic Drugs and Philip Erickson, Director of Regulatory Affairs at TEVA USA. In that conversation, Mr. Anderson requested the addition of a method and specification for testing the active ingredient's melting point. Please note that Comment A(2) made this same request, and therefore Response A(2) below addresses Mr. Anderson's request.

For ease of review, please find in **Attachment 1** a copy of the July 20, 2001 review letter for your reference. Please note that we have responded to the deficiencies in the order in which they were presented to us.

A. Deficiencies

1. There is no available pharmacopeial reference standard for Mirtazapine. As such, our

2. []

Redacted 3

Page(s) of trade

secret and /or

confidential

commercial

information

to keep the inserts neutral so as to allow for their use in multiple distributor labeled packaging. Also, please note that at the time of preparation of final print container labels, it is our format to distinguish between tablet strengths with the use of contrasting colors.

Please find in **Attachment 18** four copies of draft container labels, followed by a comparison document which calls out changes made to the labels since they were last submitted to the Agency.

Also, please find in **Attachment 19** four copies of the draft package insert, followed by a comparison document which calls out changes made to the insert since it was last submitted to the Agency.

Lastly, we acknowledge that the bioequivalence comments provided in the July 20, 2001 letter are preliminary and are subject to revision after review of the entire application. The bioequivalence comment regarding our dissolution specification is addressed in Response A(6) above (specification has been revised to NLT — (Q) in 15 minutes).

It is TEVA USA's opinion that the information presented herein represents a full and complete response to the July 20, 2001 review letter. This information is submitted for your continued review and approval of ANDA #76-119. If there are any further questions, please do not hesitate to contact me at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,



PE/asg
Enclosures



Corporate Headquarters:
TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

Phone: (215) 591 3000
FAX: (215) 591 8600

Emily Thomas
WAZ
8/1/01
30mc = 10/27/01

July 27, 2001

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

PATENT INFORMATION

NEW CORRESP

ANDA #76-119
MIRTAZAPINE TABLETS, 15 mg, 30 mg, and 45 mg
NOTIFICATION OF FILING OF LEGAL ACTION FOR PATENT INFRINGEMENT

Dear Mr. Buehler:

We submit herewith new correspondence to the above-referenced pending abbreviated new drug application to notify the Agency of a June 8, 2001 correspondence from Basil J. Lewris of Finnegan, Henderson, Farabow, Garrett & Dunner, L.L.P. on behalf of Akzo Nobel N.V. (Akzo) and Organon Inc. (Organon). Specifically the letter serves to notify us that Akzo and Organon have filed an action of patent infringement against Teva in the United States District Court for the District of New Jersey. Akzo and Organon believe that Teva's submission of ANDA #76-119 which seeks approval for the commercial manufacture, use, or sale of mirtazapine tablets before the expiration of United States Patent No. 5,977,099 infringes on United States Patent No. 5,977,099. Please find the June 8, 2001 letter enclosed for ease of review.

Should there be any questions regarding the information contained herein, please do not hesitate to contact me by phone at (215) 591-3141 or by facsimile at (215) 591-8812.

Sincerely,



PE/asg
Enclosures

Please file in latest open archival volume 76-119

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

June 8, 2001

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

**HAND DELIVERY VIA
WASHINGTON EXPRESS
SERVICES, INC.**

*Noted:
m. Aderson
N/A
A 6/23/01*

Attn: Mr. Gregory Davis

NEW CORRESP

NC

Mirtazapine Tablets, 15 mg, 30 mg, and 45 mg
Abbreviated New Drug Application No. 76-119
Notification of Filing of Legal Action for Patent Infringement

*Amel Adams
N/A
6/20/01*

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) Christopher Pelloni, Vice President, Research & Development of Teva Pharmaceuticals USA, Inc. (Teva), sent a letter to Akzo Nobel dated April 24, 2001, providing information pursuant to 21 U.S.C. § 355(j)(2)(B)(ii). Based on that letter, we provide the following information

- (i) Teva submitted to the FDA an abbreviated new drug application (ANDA) which seeks approval to engage in the commercial manufacture, use, or sale of mirtazapine tablets 15 mg, 30 mg and 45 mg before the expiration date of U.S. Patent No. 5,977,099.
- (ii) The ANDA number is ANDA 76-119.
- (iii) The name of the proposed drug product is mirtazapine tablets, 15 mg, 30 mg and 45 mg.
- (iv) The active ingredient, strength, and dosage form of the proposed drug product is mirtazapine 15 mg, 30 mg, and 45 mg tablets for oral administration.



ML

Food and Drug Administration

June 8, 2001

Page 2

- (v) The patent number and expiration date of the patent which Teva alleges to be invalid, unenforceable, or not infringed is United States Patent No. 5,977,099, which expires June 16, 2017.
- (2) Organon received Teva's letter on or about April 27, 2001.

CERTIFICATION

We hereby certify that on June 6, 2001, Akzo and Organon filed an action for patent infringement against Teva in the United States District Court for the District of New Jersey (Civil Action No. 01-2682 (FSH)). Akzo and Organon state, among other things, that under 35 U.S.C. § 271(e)(2)(A) Teva's submission to the FDA of an ANDA to obtain approval for the commercial manufacture, use, or sale of 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 Teva's ANDA for 15 mg, 30 mg, and 45 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)(4)(B)(iii), subject to an appropriate ruling by the Court.

Sincerely,

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

By: 
Basil J. Lewis

BJL/kd

cc: Christopher Pelloni (via first class mail)
Vice President, Research & Development
TEVA Pharmaceuticals USA, Inc.
1090 Horsham Road
P. O. Box 1090
North Wales, PA 19454-1090





Corporate Headquarters:
TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

Phone: (215) 591 3000
FAX: (215) 591 8600

May 11, 2001

NEW CORRESP

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

PATENT INFORMATION

151
NPT
3/22/01

ANDA #76-119
MIRTAZAPINE TABLETS, 15 mg, 30 mg, and 45 mg
RECEIPT OF NOTICE UNDER SECTION 505(j)(2)(B)(I) AND 21 CFR 314.95

Dear Mr. Buehler:

In accord with 21 CFR 314.95 (e), TEVA Pharmaceuticals USA provides herein documentation of the receipt of Notice of Certification for U.S. Patent No. 5,977,099. The Notices, sent to Organon Inc., USA and Akzo Nobel, N.V. (the affected NDA holder and patent owner, respectively), were received on April 27, 2001. This date is evidenced by the attached copies of the return receipts. In accord with 314.95(f), the first day of the 45-day period provided for in section 505(j)(4)(B)(iii) of the Act is April 28, 2001, the first day after receipt of notice. The 45-day period will therefore end on June 11, 2001.

Should there be any questions regarding the information contained herein, please do not hesitate to contact me by phone at (215) 591-3141 or by facsimile at (215) 591-8812.

Sincerely,

PE/asm
Enclosures





Corporate Headquarters:
TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

Phone: (215) 591 3000
FAX: (215) 591 8600

May 2, 2001

alstet. NAF.
ICL
5/8/01

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

PATENT INFORMATION

NEW CORRESP
NC

ICL
WAF
7/25/01

ANDA #76-119
MIRTAZAPINE TABLETS, 15 mg, 30 mg, and 45 mg
NOTICE OF CERTIFICATION OF NON-INFRINGEMENT

Dear Mr. Buehler:

TEVA Pharmaceuticals USA hereby certifies that a Notice of Certification of Non-Infringement of U.S. Patent No. 5,977,099 was provided to Organon Inc., USA as the holder of NDA # 020415 for Remeron® (mirtazapine) Tablets and Akzo Nobel, N.V., owner of the patent in accord with 314.95(b). The notices dated April 24, 2001 contain the information as required under 314.95(c). A copy of the notices are provided herein.

Should there be any questions regarding the information contained herein, please do not hesitate to contact me by phone at (215) 591-3141 or by facsimile at (215) 591-8812.

Sincerely,

Philip Erickson

PE/asg
Enclosures



MD
5-8-01



Corporate Headquarters:
TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

Phone: (215) 591 3000
FAX: (215) 591 8600

April 12, 2001

ORIG AMENDMENT

AB

**BIOEQUIVALENCY
TELEPHONE AMENDMENT**

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ANDA #76-119
MIRTAZAPINE TABLETS, 15 mg, 30 mg, and 45 mg
BIOEQUIVALENCY TELEPHONE AMENDMENT - RESPONSE TO APRIL 11, 2001
TELEPHONE CONTACT

Dear Mr. Buehler:

We submit herewith a bioequivalency telephone amendment to the above-referenced pending abbreviated new drug application in response to an April 11, 2001 telephone conversation between Krista Scardina of the Office of Generic Drugs and Philip Erickson, Director Regulatory Affairs. Per your request for long-term freezer stability data of Mirtazapine in human plasma over a seventy-eight (78) day period, please find attached long-term freezer stability data of Mirtazapine in human plasma which covers an eighty-four (84) day period.

It is TEVA USA's opinion that the information presented herein represents a full and complete response to the April 11, 2001 telephone contact. This information is submitted for your continued review and approval of ANDA #76-119. If there are any further questions, please do not hesitate to contact me at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,

PE/asg
Enclosures



MAR 12 2001

TEVA Pharmaceuticals USA
Attention: Philip Erickson
1090 Horsham Road
P.O. Box 1090
North Wales, PA 19454
|||||

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, 15 mg, 30 mg and 45 mg

DATE OF APPLICATION: February 26, 2001

DATE (RECEIVED) ACCEPTABLE FOR FILING: February 26, 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.

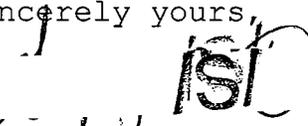
We will correspond with you further after we have had the opportunity to review the application.

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,


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