CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

76-241

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

Sponsor: Amide Pharmaceutical, Inc.

Approval Date: June 25, 2003

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 76-241

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

76-241

APPROVAL LETTER

ANDA 76-241

JUN 25 2003

Amide Pharmaceutical, Inc.
Attention: Jasmine Shah
101 East Main Street
Little Falls, NJ 07424

Dear Sir:

This is in reference to your abbreviated new drug application (ANDA) dated September 21, 2001, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Mirtazapine Tablets, 15 mg, 30 mg, and 45 mg.

Reference is also made to our tentative approval letter dated February 12, 2003, and to your amendments dated May 28, and June 11, 2003. We also acknowledge receipt of your correspondence dated June 20, 2003, addressing patent issues explained in further detail below.

The listed drug product referenced in your application, Remeron Tablets of Organon Inc., appears to be subject to a period of patent protection. As noted in the agency's publication entitled Approved Drug Products with Therapeutic Equivalence Evaluations, the "Orange Book", U.S. patent 5,977,099 (the '099 patent) is scheduled to expire on June 16, 2017. Your application contains a paragraph IV certification to the '099 patent under Section 505(j)(2)(A)(vii)(IV) of the Act stating that your manufacture, sale, or use of Mirtazapine Tablets will not infringe on this patent. 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 Amide Pharmaceutical, Inc. (Amide) for infringement of the '099 patent which was the subject of the paragraph IV certification. This action must be brought against Amide prior to the expiration of forty-five (45) days from the date the notice you provided under paragraph (2)(B)(i) was received by the NDA/patent holder(s). You notified the agency that Amide complied with the requirements of Section 505(j)(2)(B) of the Act, and that a patent infringement action was initiated in the United States District Court for the District of New Jersey (Azko Nobel N.V.

and Organon Inc. v. Amide Pharmaceutical, Inc., Civil Action No. 02-CV0190-FSH). You subsequently informed the agency that the court entered a dismissal (with prejudice) of the above litigation into the docket. This dismissal represented an adjudication of non-infringement of the '099 patent.

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

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

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

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

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

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

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

Sincerely yours,

/S/ for 6/25/2003

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

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

76-241

TENTATIVE APPROVAL LETTER(S)

ANDA 76-241

FEB 12 2003

Amide Pharmaceutical, Inc.
Attention: Jasmine Shah
101 East Main Street
Little Falls, NJ 07424

Dear Sir:

This is in reference to your abbreviated new drug application (ANDA) dated September 20, 2001, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Mirtazapine Tablets, 15 mg, 30 mg, and 45 mg.

Reference is also made to your amendments dated June 6, August 20, August 26, October 21, November 8, and December 30, 2002; and January 14, 2003. Reference is also made to your correspondence dated January 14, December 11, and December 19, 2002, pertaining to patent issues associated with the reference listed drug product.

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. Although we are unable to grant final approval to your application because of issues related to (1) a listed patent which resulted in the ongoing litigation explained below, and (2) 180-day generic drug exclusivity, 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.

The listed drug product (RLD) referenced in your application, Remeron® Tablets of Organon Inc., is subject to a period of patent protection and exclusivity. As noted in the agency's publication entitled Approved Drug Products with Therapeutic Equivalence Evaluations, U.S. patent 5,977,099, (the '099 patent) is due 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 and/or unenforceable, and/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 ANDA shall be made effective immediately, unless an action is brought against Amide Pharmaceutical, Inc. (Amide) for infringement of the '099 patent. Such action must be brought against Amide prior to the expiration of forty-five (45) days from the date your notification was received by the NDA/patent holder. You have notified the agency that Amide complied with the requirements of Section 505(j)(2)(B) of the Act and that as a result litigation is underway in the United States District Court for the District of New Jersey involving a challenge to the '099 patent (Organon Inc. and Akzo Nobel N.V. v. Amide Pharmaceutical, Inc., Civil Action No. 02-CV0190-FSH). Therefore, with respect to this patent litigation, final approval may not 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 '099 patent has expired, and

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

However, the Act also provides that approval of an ANDA that contains a paragraph IV certification, and that provides for approval of the same drug product as that for which another ANDA containing a paragraph IV certification was previously received, shall be made effective not earlier than one hundred and eighty (180) days after:

1. the date the Secretary receives notice from the applicant of the previous application that commerical marketing of the drug product approved in that application was initiated, or

2. the date of a decision of a court holding the '099 patent to be invalid or not infringed; whichever option occurs first (Section 505(j)(5)(B)(iv).

With regard to Mirtazapine Tablets, 15 mg, 30 mg, and 45 mg, the Office of Generic Drugs received and filed ANDAs from other applicants containing paragraph IV certifications to the '099 patent for each strength prior to the filing of your application. Accordingly, your application will not be eligible for full approval until 180 days following the earlier of event 1. or 2. noted in the above paragraph. We refer you to the agency's guidance document entitled "180-Day Generic Drug Exclusivity Under the Hatch-Waxman Amendments" (June 1998), for additional information.

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 to document the start/end of the 180-day generic drug exclusivity period, 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 Nicole Park, Pharm.D., Project Manager, at 301-827-5798.

Sincerely yours,

/S/

Gary Buehler 2/12/03
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

76-241

FINAL PRINTED LABELING(S)

8220-04

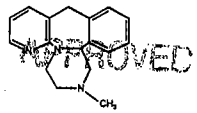
MIRTAZAPINE TABLETS

Rx Only

APPROVED
JUN 25 2003

DESCRIPTION

Mirtazapine Tablets are an orally administered drug. Mirtazapine has a tetracyclic chemical structure and belongs to the piperazino-azepine group of compounds. It is designated 1,2,3,4,10,14b-hexahydro-2-methylpyrazino[2,1-a] pyrido [2,3-c] benzazepine and has the molecular formula of $C_{17}H_{19}N_3$. Its molecular weight is 265.36. The structural formula is the following and it is the racemic mixture:



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

Mirtazapine is supplied for oral administration as scored film-coated tablets containing 15 or 30 mg of mirtazapine, and unscored film-coated tablets containing 45 mg of mirtazapine. Each tablet also contains carnauba wax powder, colloidal silicon dioxide, corn starch, hydroxypropyl methylcellulose (15 mg and 30 mg tablet), lactose monohydrate, magnesium stearate, microcrystalline cellulose, polydextrose, polyethylene glycol, synthetic red iron oxide (30 mg tablet) and synthetic yellow iron oxide (15 mg tablet), titanium dioxide, and triacetin.

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-HT_2 and 5-HT_3 receptors. Mirtazapine has no significant affinity for the 5-HT_{1A} and 5-HT_{1B} receptors.

Mirtazapine is a potent antagonist of histamine (H_1) receptors, a property that may explain its prominent sedative effects. Mirtazapine is a moderate peripheral α_1 adrenergic antagonist, a property that may explain the occasional orthostatic hypotension reported in association with its use.

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

Pharmacokinetics

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

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

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

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

Special Populations

Geriatric

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

Pediatrics

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

Gender

The mean elimination half-life of mirtazapine after oral administration ranges from approximately 20 to 40 hours across age and gender subgroups, with females of all ages exhibiting significantly longer elimination half-lives than males (mean half-life of 37 hours for females vs. 26 hours for males) (see Pharmacokinetics).

Race

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

Renal Insufficiency

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

Hepatic Insufficiency

Following a single 15 mg oral dose of mirtazapine, the oral clearance of mirtazapine was decreased by approximately 30% in hepatically impaired patients compared to subjects with normal hepatic function. Caution is indicated in administering mirtazapine to patients with compromised hepatic function (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Clinical Trials Showing Effectiveness

The efficacy of mirtazapine tablets as a treatment for major depressive disorder was established in four placebo-controlled, 6-week trials in adult outpatients meeting DSM-III criteria for major depressive disorder. Patients were titrated with mirtazapine from a dose range of 5 mg up to 35 mg/day. Overall, these studies demonstrated mirtazapine to be superior to placebo on at least three of the following four measures: 21-item Hamilton Depression Rating Scale (HDRS) total score; HDRS Depressed Mood item; CGI Severity score; and Montgomery and Asberg Depression Rating Scale (MADRS). Superiority of mirtazapine over placebo was also found for certain factors of the HDRS, including anxiety/somatization factor and sleep disturbance factor. The mean mirtazapine dose for patients who completed these four studies ranged from 21 to 32 mg/day. A fifth study of similar design utilized a higher dose (up to 50 mg) per day and also showed effectiveness.

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

INDICATIONS AND USAGE

Mirtazapine Tablets are indicated for the treatment of major depressive disorder.

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

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

The effectiveness of mirtazapine in hospitalized depressed patients has not been adequately studied. The physician who elects to use mirtazapine for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient.

CONTRAINDICATIONS

Mirtazapine Tablets are contraindicated in patients with a known hypersensitivity to mirtazapine.

WARNINGS

Agranulocytosis

In premarketing clinical trials, two (one with Sjögren's Syndrome) out of 2,796 patients treated with mirtazapine tablets developed agranulocytosis (absolute neutrophil count (ANC) < 500/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 tablets, it is recommended that mirtazapine not be used in combination with an MAOI, or within 14 days of initiating or discontinuing therapy with an MAOI.

PRECAUTIONS

General

Somnolence

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

Dizziness

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

Increased Appetite/Weight Gain

In U.S. controlled studies appetite increase was reported in 17% of patients treated with mirtazapine, compared to 2% for placebo and 6% for amitriptyline. In these same trials, weight gain of ≥ 7% of body weight was reported in 7.5% of patients treated with mirtazapine, compared to 0% for placebo and 5.9% for amitriptyline. In a pool of premarketing U.S. studies, including many patients for long-term, open label treatment, 8% of patients receiving mirtazapine discontinued for weight gain. In an 8-week long pediatric clinical trial of doses between 15-45 mg/day, 49% of mirtazapine-treated patients had a weight gain of at least 7%, compared to 5.7% of placebo treated patients (see PRECAUTIONS-Pediatric Use).

Cholesterol/Triglycerides

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

Transaminase Elevations

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

Activation of Mania/Hypomania

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

Seizure

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

Suicide

Suicidal ideation is inherent in major depressive disorder and may persist until significant remission occurs. As with any patient receiving drugs effective in the treatment of major depressive disorder, high-risk patients should be closely supervised during initial drug therapy. Prescriptions of mirtazapine should be written for the smallest quantity consistent with good patient management, in order to reduce the risk of overdose.

Use in Patients with Concomitant Illness

Clinical experience with mirtazapine in patients with concomitant systemic illness is limited. Accordingly, care is advisable in prescribing mirtazapine for patients with diseases or conditions that affect metabolism or hemodynamic responses.

Mirtazapine has not been systematically evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or other significant heart disease. Mirtazapine was associated with significant orthostatic hypotension in early clinical pharmacology trials with normal volunteers. Orthostatic hypotension was infrequently observed in clinical trials with depressed patients. Mirtazapine should be used with caution in patients with known cardiovascular or cerebrovascular disease that could be exacerbated by hypotension (history of myocardial infarction, angina, or ischemic stroke) and conditions that would predispose patients to hypotension (dehydration, hypovolemia, and treatment with antihypertensive medication).

Mirtazapine clearance is decreased in patients with moderate [glomerular filtration rate (GFR) = 11 to 39 mL/min/1.73 m^2] and severe [GFR < 10 mL/min/1.73 m^2] renal impairment, and also in patients with hepatic impairment. Caution is indicated in administering mirtazapine to such patients (see CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION).

Information for Patients

Physicians are advised to discuss the following issues with patients for whom they prescribe Mirtazapine Tablets:

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, patients should be advised to avoid alcohol while taking mirtazapine.

Pregnancy

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

Nursing

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

Laboratory Tests

There are no routine laboratory tests recommended.

Drug Interactions

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

Drugs Affecting Hepatic Metabolism

The metabolism and pharmacokinetics of mirtazapine tablets may be affected by the induction or inhibition of drug-metabolizing enzymes.

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

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

Alcohol

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

Diazepam

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

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

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

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

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

Impairment of Fertility
In a fertility study in rats, mirtazapine was given at doses up to 100 mg/kg (20 times the maximum recommended human dose (MRHD) on a mg/m^2 basis). Mating and conception were not affected by the drug, but estrous cycling was disrupted at doses that were 3 or more times the MRHD and pre-implantation losses occurred at 20 times the MRHD.

Pregnancy
Teratogenic Effects- Pregnancy Category C
Reproduction studies in pregnant rats and rabbits at doses up to 100 mg/kg and 40 mg/kg, respectively (20 and 17 times the maximum recommended human dose (MRHD) on a mg/m^2 basis, respectively), have revealed no evidence of teratogenic effects. However in rats, there was an increase in post implantation losses in dams treated with mirtazapine. There was an increase in pup deaths during the first 3 days of lactation and a decrease in pup birth weights. The cause of these deaths is not known. These effects occurred at doses that were 20 times the MRHD, but not at 3 times the MRHD, on a mg/m^2 basis. There are no adequate and well controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers
It is not known whether mirtazapine is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when mirtazapine tablets are administered to nursing women.

Pediatric Use
Safety and effectiveness in pediatric patients have not been established. In an 8-week long pediatric clinical trial of doses between 15-45 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 tablets. This drug is known to be substantially excreted by the kidney (75%), and the risk of decreased clearance of this drug is greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection. Sedating drugs may cause confusion and over-sedation in the elderly. No unusual adverse age-related phenomena were identified in this group. Pharmacokinetic studies revealed a decreased clearance in the elderly. Caution is indicated in administering mirtazapine to elderly patients (see CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION).

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

Common Adverse Events Associated with Discontinuation of Treatment in 6-Week U.S. Mirtazapine tablet Trials

Adverse Event	Percentage of Patients Discontinuing with Adverse Event	
	Mirtazapine tablets (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 tablets (incidence of 5% or greater) and not observed at an equivalent incidence among placebo-treated patients mirtazapine incidence at least twice that for placebo) were:

Common Treatment-Emergent Adverse Events Associated with the Use of mirtazapine tablets in 6-week U.S. Trials

Adverse Event	Percentage of Patients Reporting Adverse Event	
	Mirtazapine tablets (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 tablets treated patients who participated in short-term U.S. placebo controlled trials in which patients were dosed in a range of 5 to 60 mg/day. This table shows the percentage of patients in each group who had at least one episode of an event at some time during their treatment. Reported adverse events were classified using a standard COSTART-based dictionary terminology.
The prescriber should be aware that these figures cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those which prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other investigations involving different treatments, uses and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and non-drug factors to the side effect incidence rate in the population studied.

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

Body System Adverse Clinical Experience	Mirtazapine tablets (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 tablets are included, except the following events which had an incidence on placebo ≥ mirtazapine tablets: headache, infection, pain, chest pain, palpitation, tachycardia, postural hypotension, nausea, dyspepsia, diarrhea, flatulence, insomnia, nervousness, libido decreased, hypertonia, pharyngitis, rhinitis, sweating, amblyopia, tinnitus, taste perversion.

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

Other Adverse Events Observed During the Premarketing Evaluation of Mirtazapine
During its premarketing assessment, multiple doses of mirtazapine tablets were administered to 2,796 patients in clinical studies. The conditions and duration of exposure to mirtazapine varied greatly, and included (in overlapping categories) open and double-blind studies, uncontrolled and controlled studies, inpatient and outpatient studies, fixed dose and titration studies. Untoward events associated with this exposure were recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of untoward events into a smaller number of standardized event categories.
In the tabulations that follow, reported adverse events were classified using a standard COSTART-based dictionary terminology. The frequencies presented, therefore, represent the proportion of the 2,796 patients exposed to multiple doses of mirtazapine who experienced an event of the type cited on at least one occasion while receiving mirtazapine. All reported events are included except those already listed in the previous table, those adverse experiences subsumed under COSTART terms that are either overly general or excessively specific so as to be uninformative, and those events for which a drug cause was very remote.
It is important to emphasize that, although the events reported occurred during treatment with mirtazapine, they were not necessarily caused by it.
Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse events are those occurring on one or more occasions in at least 1/100 patients; infrequent adverse events are those occurring in 1/100 to 1/1000 patients; rare events are those occurring in fewer than 1/1000 patients. Only those events not already listed in the previous table appear in this listing. Events of major clinical importance are also described in the WARNINGS and PRECAUTIONS sections.

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

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

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

Endocrine System: *rare:* goiter, hypothyroidism.

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

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

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

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

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

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

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

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

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

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

Overdose Management
Treatment should consist of those general measures employed in the management of overdose with any drug effective in the treatment of major depressive disorder.
Ensure an adequate airway, oxygenation, and ventilation. Monitor cardiac rhythm and vital signs. General supportive and symptomatic measures are also recommended. Induction of emesis is not recommended. Gastric lavage with a large-bore orogastric tube with appropriate airway protection, if needed, may be indicated if performed soon after ingestion, or in symptomatic patients.
Activated charcoal should be administered. There is no experience with the use of forced diuresis, dialysis, hemoperfusion or exchange transfusion in the treatment of mirtazapine overdosage. No specific antidotes for mirtazapine are known.
In managing overdosage, consider the possibility of multiple drug involvement. The physician should consider contacting a poison control center for additional information on the treatment of any overdose. Telephone numbers for certified poison control centers are listed in the *Physicians' Desk Reference (PDR).*

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

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

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

Switching Patients To or From a Monoamine Oxidase Inhibitor
At least 14 days should elapse between discontinuation of an MAOI and initiation of therapy with Mirtazapine Tablets. In addition, at least 14 days should be allowed after stopping mirtazapine before starting an MAOI.

HOW SUPPLIED
Mirtazapine Tablets are supplied as:

15 mg Tablets-Yellow colored, modified oval shaped film coated tablets, debossed "A226" on one side and bisect on the other. Supplied in bottles of 30's, 500's and 100's (10 x 10) unit-dose tablets.

30 mg Tablets-Tan colored, modified oval shaped film coated tablets, debossed "A227" on one side and bisect on the other. Supplied in bottles of 30's, 500's and 100's (10 x 10) unit-dose tablets.

45 mg Tablets-White colored, modified oval shaped film coated tablets, debossed "A228" on one side. Supplied in bottles of 30's, 500's and 100's (10 x 10) unit-dose tablets.

Store at controlled room temperature 15° to 30°C (59° to 86°F) [See USP]. Protect from light and moisture.

Dispense in tight, light-resistant container as defined in the USP.

MANUFACTURED BY
AMIDE PHARMACEUTICAL, INC.
11/02 101 East Main Street Little Falls, NJ 07424 USA

Amide
PHARMACEUTICAL, INC.

NDC 52152-226-30

MIRTAZAPINE TABLETS 15 mg

APPROVED

JUN 25 2003

Rx only

30 TABLETS

Each Tablet Contains:
Mirtazapine ..... 15 mg

Usual Dosage: Read enclosed prescribing information.

Store at controlled room temperature 15°-30°C (59°-86°F) [See USP].

Dispense in tight, light-resistant container as defined in the USP.

Yellow colored, modified oval shaped film coated tablets, debossed "A226" on one side and bisect on the other.

N 3 52152-226-30 3

AMIDE PHARMACEUTICAL, INC.
101 East Main Street
Little Falls, NJ 07424 USA

Control No.:
Exp. Date:

8211-01

Amide
PHARMACEUTICAL, INC.

NDC 52152-226-11

MIRTAZAPINE TABLETS 15 mg

JUN 25 2003

APPROVED

Rx only

100 Unit-Dose Tablets (10 x 10)

N 3 52152-226-11 2

Each Tablet Contains:
Mirtazapine ..... 15 mg

Usual Dosage: Read enclosed prescribing information.

Store at controlled room temperature 15°-30°C (59°-86°F) [See USP].

Yellow colored, modified oval shaped film coated tablets, debossed "A226" on one side and bisect on the other.

This unit-dose package is not child-resistant. If dispensed for outpatient use, a child-resistant container should be used.

PROTECT FROM LIGHT AND MOISTURE.

AMIDE PHARMACEUTICAL, INC.
101 East Main Street
Little Falls, NJ 07424 USA

Control No.:
Exp. Date:
8213-01

Amide
PHARMACEUTICAL, INC.

NDC 52152-226-11

MIRTAZAPINE TABLETS 15 mg

APPROVED

JUN 25 2003

Rx only

100 Unit-Dose Tablets (10 x 10)

N 3 52152-226-11 2

Each Tablet Contains:
Mirtazapine ..... 15 mg

Usual Dosage: Read enclosed prescribing information.

Store at controlled room temperature 15°-30°C (59°-86°F) [See USP].

Yellow colored, modified oval shaped film coated tablets, debossed "A226" on one side and bisect on the other.

This unit-dose package is not child-resistant. If dispensed for outpatient use, a child-resistant container should be used.

PROTECT FROM LIGHT AND MOISTURE.

AMIDE PHARMACEUTICAL, INC.
101 East Main Street
Little Falls, NJ 07424 USA

Control No.:
Exp. Date:
8213-01

Amide
PHARMACEUTICAL, INC.

NDC 52152-226-04

MIRTAZAPINE TABLETS 15 mg

APPROVED

JUN 25 2003

Rx only

500 TABLETS

Each Tablet Contains:
Mirtazapine ..... 15 mg

Usual Dosage: Read enclosed prescribing information.

Store at controlled room temperature 15°-30°C (59°-86°F) [See USP].

Dispense in tight, light-resistant container as defined in the USP.

Yellow colored, modified oval shaped film coated tablets, debossed "A226" on one side and bisect on the other.

N 3 52152-226-04 4

AMIDE PHARMACEUTICAL, INC.
101 East Main Street
Little Falls, NJ 07424 USA

Control No.:
Exp. Date:

8212-01

Amide
PHARMACEUTICAL, INC.

NDC 52152-228-30

MIRTAZAPINE TABLETS

45 mg

APPROVED
JUN 25 2003

Rx only

30 TABLETS

Each Tablet Contains:
Mirtazapine ..... 45 mg

Usual Dosage: Read enclosed prescribing information.

Store at controlled room temperature 15°-30°C (59°-86°F) [See USP].

Dispense in tight, light-resistant container as defined in the USP.

White colored, modified oval shaped film coated tablets, debossed "A228" on one side.

N 3 52152-228-30 7

AMIDE PHARMACEUTICAL, INC.
101 East Main Street
Little Falls, NJ 07424 USA

Control No.:
Exp. Date:

8217-01

Amide
PHARMACEUTICAL, INC.

NDC 52152-228-11

MIRTAZAPINE TABLETS

45 mg

JUN 25 2003
APPROVED

Rx only

100 Unit-Dose Tablets (10 x 10)

N 3 52152-228-11 6

Each Tablet Contains:
Mirtazapine ..... 45 mg

Usual Dosage: Read enclosed prescribing information.

Store at controlled room temperature 15°-30°C (59°-86°F) [See USP].

White colored, modified oval shaped film coated tablets, debossed "A228" on one side.

This unit-dose package is not child-resistant. If dispensed for outpatient use, a child-resistant container should be used.

PROTECT FROM LIGHT AND MOISTURE.

AMIDE PHARMACEUTICAL, INC.
101 East Main Street
Little Falls, NJ 07424 USA

Control No.:
Exp. Date:
8219-01

Amide
PHARMACEUTICAL, INC.

NDC 52152-228-04

MIRTAZAPINE TABLETS

45 mg

JUN 25 2003
APPROVED

Rx only

500 TABLETS

Each Tablet Contains:
Mirtazapine ..... 45 mg

Usual Dosage: Read enclosed prescribing information.

Store at controlled room temperature 15°-30°C (59°-86°F) [See USP].

Dispense in tight, light-resistant container as defined in the USP.

White colored, modified oval shaped film coated tablets, debossed "A228" on one side.

N 3 52152-228-04 8

AMIDE PHARMACEUTICAL, INC.
101 East Main Street
Little Falls, NJ 07424 USA

Control No.:
Exp. Date:

8218-01

Mirtazapine Tablet 15 mg NDC# 52152-XXX-XX Control # XXXXXX Exp Date: MM/YYYY Amide Pharmaceutical, Inc. Little Falls, NJ 07424	**Mirtazapine Tablet 15 mg** NDC# 52152-XXX-XX Control # XXXXXX Exp Date: MM/YYYY Amide Phamaceutical, Inc. Little Falls, NJ 07424
Mirtazapine Tablet 15 mg NDC# 52152-XXX-XX Control # XXXXXX Exp Date: MM/YYYY Amide Pharmaceutical, Inc. Little Falls, NJ 07424	**Mirtazapine Tablet 15 mg** NDC# 52152-XXX-XX Control # XXXXXX Exp Date: MM/YYYY Amide Phamaceutical, Inc. Little Falls, NJ 07424
Mirtazapine Tablet 15 mg NDC# 52152-XXX-XX Control # XXXXXX Exp Date: MM/YYYY Amide Pharmaceutical, Inc. Little Falls, NJ 07424	**Mirtazapine Tablet 15 mg** NDC# 52152-XXX-XX Control # XXXXXX Exp Date: MM/YYYY Amide Phamaceutical, Inc. Little Falls, NJ 07424
Mirtazapine Tablet 15 mg NDC# 52152-XXX-XX Control # XXXXXX Exp Date: MM/YYYY Amide Pharmaceutical, Inc. Little Falls, NJ 07424	**Mirtazapine Tablet 15 mg** NDC# 52152-XXX-XX Control # XXXXXX Exp Date: MM/YYYY Amide Phamaceutical, Inc. Little Falls, NJ 07424
Mirtazapine Tablet 15 mg NDC# 52152-XXX-XX Control # XXXXXX Exp Date: MM/YYYY Amide Pharmaceutical, Inc. Little Falls, NJ 07424	**Mirtazapine Tablet 15 mg** NDC# 52152-XXX-XX Control # XXXXXX Exp Date: MM/YYYY Amide Phamaceutical, Inc. Little Falls, NJ 07424

APPROVED JUN 2 5 2003

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

76-241

CSO LABELING REVIEW(S)

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

ANDA Number: **76-241** **Date of Submission: November 8, 2002**

Applicant's Name: **Amide Pharmaceutical, Inc.**

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

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):
Do you have 12 Final Printed Labels and Labeling? Yes No If no, list why:
Container Labels: 15 mg, 30 mg and 45 mg (30s, and 500s)
Satisfactory in FPL as of the June 6, 2002 submission (Vol 2.1 Attachment 6).
Unit Dose Blister Labels: 15 mg, 30 mg and 45 mg (2x5)
Satisfactory in FPL as of the November 8, 2002 submission (Vol 3.1 Attachment 2).
Unit Dose Carton Labeling: 15 mg, 30 mg and 45 mg 100s (10x10)]
Satisfactory in FPL as of the June 6, 2002 submission (Vol 2.1 Attachment 6).
Professional Package Insert Labeling:
Satisfactory in FPL as of the November 8, 2002 submission (Vol 3.1 Attachment 2)[Code8220-04;Rev: 11/02].
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 #: 9/30/02 (S-015) and 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® (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:

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

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.

3. Amide is the manufacturer (p 3166 v B 1.1).

4. The drug product will be made available in container sizes of 30s (CRC), 500s (non-CRC), and unit dose 100s (10 x 10). The RLD is available in container sizes of 30s (all three strengths), 100s (15 mg and 30 mg), and UD 100s (15 mg and 30 mg).

5. The inactives are accurately listed in the DESCRIPTION section (pp 3012- 3014 v B 1.1).

6. The tablet descriptions are accurate as seen in the HOW SUPPLIED section (pp 3727, 3731, 3735 v B 1.2).

7. Storage Conditions:
NDA – Store at 25°C (77°F);excursions permitted to 15°-30°C (59°-86°F)[see USP Controlled Room Temperature]. Protect from light and moisture
ANDA – Store at controlled room temperature 15° - 30°C (59° - 86°F)[see USP].
USP – not USP

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

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

Date of Review: **November 26, 2002** **Date of Submission:** **11-08-02**

Primary Reviewer: **Michelle Dillahunt** **Date:** 12/4/02

/S/

Team Leader: **Lillie Golson** **Date:** 12/4/02

/S/

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cc: ANDA: 76-241
DUP/DIVISION FILE
HFD-613/MDillahunt/LGolson (no cc)
V:\FIRMSAM\AMIDE\LTRS&REV\76241ap.l
Review

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

ANDA Number: **76-241** **Date of Submission: October 21, 2002**

Applicant's Name: **Amide Pharmaceutical, Inc.**

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

Labeling Deficiencies:

1. Blister: Ensure that the established name and strength appear as the most prominent information.

2. INSERT

Due to changes in the insert labeling of the reference listed drug, (Remeron® (NDA 20-415) - Organon, Inc, approved September 30, 2002), please revise your labeling as follows:

PRECAUTIONS

a. Increased Appetite/Weight Gain

Please add the following sentence as the last sentence;

In an 8-week long pediatric clinical trial of doses between 15-45 mg/day, 49% of mirtazapine-treated patients had a weight gain of at least 7%, compared to 5.7% of placebo treated patients (see PRECAUTIONS-Pediatric Use).

b Pediatric Use

Please add the following sentence as the last sentence;

In an 8-week long pediatric clinical trial of doses between 15-45 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).

Please revise your unit dose blister 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 revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address -

http://www.fda.gov/cder/cdernew/listserv.html

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

/S/

Wm Peter Rickman
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 500s
Satisfactory in FPL as of the June 6, 2002 submission (Vol 2.1 Attachment 6).
Unit Dose Blister Labels:
Unit Dose Carton Labeling:
Satisfactory in FPL as of the June 6, 2002 submission (Vol 2.1 Attachment 6).
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 #: 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? 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 9/30/02 (NDA 20-415/S-015). The supplement provides for additions to the PRECAUTIONS statement. The firm has been asked to revise their insert labeling.
The model labeling has been revised by the Division of Neuropharmacological Drug Products for the generics due to M-18 exclusivity. Adolph Vezza faxed the model labeling to all of the generics firms with applications for mirtazapine.
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:

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

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. Amide is the manufacturer (p 3166 v B 1.1).

4. The drug product will be made available in container sizes of 30s (CRC), 500s (non-CRC), and unit dose 100s (10 x 10). The RLD is available in container sizes of 30s (all three strengths), 100s (15 mg and 30 mg), and UD 100s (15 mg and 30 mg).

5. The inactives are accurately listed in the DESCRIPTION section (pp 3012- 3014 v B 1.1).

6. The tablet descriptions are accurate as seen in the HOW SUPPLIED section (pp 3727, 3731, 3735 v B 1.2).

7. Storage Conditions:
NDA – Store at controlled room temperature 20°-25°C (68°-77°F).
ANDA – Store at controlled room temperature 15° - 30°C (59° - 86°F)[see USP].
USP – not USP

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

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

Date of Review: **10-29-02** **Date of Submission:** **10-21-02**

Primary Reviewer: **Michelle Dillahunt** **Date:** 11/1/02

/S/

Team Leader: **Lillie Golson** **Date:** 11/4/02

/S/

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cc: ANDA: 76-241
DUP/DIVISION FILE
HFD-613/MDillahunt/LGolson (no cc)
V:\FIRMSAM\AMIDE\LTRS&REV\76241na4.l
Review

APPEARS THIS WAY
ON ORIGINAL

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

ANDA Number: **76-241** **Date of Submission:** **August 26, 2002**

Applicant's Name: **Amide Pharmaceutical, Inc.**

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

Labeling Deficiencies:

1. UNIT DOSE BLISTER

   a. We encourage the inclusion of a NDC number on your unit dose blister labels.

   b. Please increase the font size of your established name and strength.

2. INSERT

   a. GENERAL COMMENTS

      Upon further review, we ask that you make the additional following revisions:

   b. DESCRIPTION

      i. Revise the first sentence to read: "Mirtazapine Tablets are an orally administered drug".

      ii. Revise the second and third sentence to read: "Mirtazapine has a tetracyclic chemical structure and belongs to the piperazino-azepine group of compounds."

   c. CLINICAL PHARMACOLOGY

      i. Pharmacodynamics- -first sentence; replace "[redacted] with "drugs effective in the treatment of major depressive disorder,".

      ii. Clinical Trials Showing Effectiveness-third sentence, replace "Major Depressive Disorder" with "Depression" (Hamilton Depression Rating Scale and Montgomery and Asberg Depression Rating Scale)

   d. INDICATIONS AND USAGE

      i. Third paragraph, first sentence; delete [redacted]

      ii. Third paragraph – second sentence; replace "[redacted]" with "re-evaluate".

   e. WARNINGS

      MAO Inhibitors- revise the first sentence to read;
      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.....

f. PRECAUTIONS

i. Suicide-second sentence; replace "[redacted]with "drugs effective in the treatment of major depressive disorder,"

ii. Use in Patients with Concomittant Illness-second paragraph; delete the second sentence, [redacted]

g. ADVERSE REACTIONS

Nervous System –replace "[redacted]" with "depression".

h. OVERDOSAGE

Overdosage Management, first paragraph; replace '[redacted] with "drug effective in the treatment of major depressive disorder".

i. DOSAGE AND ADMINISTRATION

Initial Treatment

Revise the second and third sentence of the first paragraph to read, "In the controlled clinical trials, establishing the efficacy of mirtazapine in the treatment of major depressive disorder, the effective dose range was generally 15-45 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".

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

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

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

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

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):
Do you have 12 Final Printed Labels and Labeling? Yes No If no, list why:
Container Labels: 30s, and 500s
Satisfactory in FPL as of the June 6, 2002 submission (Vol 2.1 Attachment 6).
Unit Dose Blister Labels:
Unit Dose Carton Labeling:
Satisfactory in FPL as of the June 6, 2002 submission (Vol 2.1 Attachment 6).
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)

1. Review based on the labeling of Remeron®, approved 4/9/02 (NDA 20-415/S-009). The model labeling has been revised by the Division of Neuropharmacological Drug Products for the

generics due to M-18 exclusivity. Adolph Vezza faxed the model labeling to all of the generics firms with applications for mirtazapine.

2. 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

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. Amide is the manufacturer (p 3166 v B 1.1).

4. The drug product will be made available in container sizes of 30s (CRC), 500s (non-CRC), and unit dose 100s (10 x 10). The RLD is available in container sizes of 30s (all three strengths), 100s (15 mg and 30 mg), and UD 100s (15 mg and 30 mg).

5. The inactives are accurately listed in the DESCRIPTION section (pp 3012- 3014 v B 1.1).

6. The tablet descriptions are accurate as seen in the HOW SUPPLIED section (pp 3727, 3731,. 3735 v B 1.2).

7. Storage Conditions:
NDA – Store at controlled room temperature 20°-25°C (68°-77°F).
ANDA – Store at controlled room temperature 15° - 30°C (59° - 86°F)[see USP].
USP – not USP

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

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

Date of Review: 9-30-02 **Date of Submission:** 8-26-02

Primary Reviewer: Michelle Dillahunt /S/ **Date:** 9/30/02

Team Leader: Lillie Golson /S/ **Date:** 9/30/02

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cc: ANDA: 76-241
DUP/DIVISION FILE
HFD-613/MDillahunt/LGolson (no cc)
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Review

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

ANDA Number: **76-241** Date of Submission: **June 6, 2002**

Applicant's Name: **Amide Pharmaceutical, Inc.**

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

Labeling Deficiencies:

1. UNIT DOSE BLISTER

   We note that you have not submitted unit dose blister labels with the revision [redacted] (rather than "Tablets') as previously directed. Please submit.

2. INSERT

   a. GENERAL COMMENTS

      i. Due to changes in the labeling of the reference listed drug, Remeron®, approved April 9, 2002, please make the revisions as seen below.

      ii. Replace the word " [redacted] with the words "major depressive disorder" throughout the insert except where indicated below.

   b. INDICATIONS AND USAGE

      i. Third paragraph - The sentence beginning "The antidepressant ..." begins a new paragraph.

      ii. Delete the sentence " [redacted]

      iii. Let the last sentence be a part of the paragraph beginning " [redacted] ..." and revise it to read "... adequately studied. The physician who ... individual patient."

   c. ADVERSE REACTIONS

      i. ECG Changes - Delete the text of this subsection and replace with the following text:

      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 $\geq$ 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.

ii. Add the following text as the last subsection of this section:

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.

d. DOSAGE AND ADMINISTRATION

Maintenance/Extended Treatment - Delete the text of this subsection and replace with the following text:

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.

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

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

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

/S/ /for/

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 500s
Satisfactory in FPL as of the June 6, 2002 submission (Vol 2.1 Attachment 6).
Unit Dose Blister Labels:
Unit Dose Carton Labeling:
Satisfactory in FPL as of the June 6, 2002 submission (Vol 2.1 Attachment 6).
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)

1. Review based on the labeling of Remeron®, approved 4/9/02 (NDA 20-415/S-009).

2. 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) which relates to 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. Amide is the manufacturer (p 3166 v B 1.1).

4. The drug product will be made available in container sizes of 30s (CRC), 500s (non-CRC), and unit dose 100s (10 x 10). The RLD is available in container sizes of 30s (all three strengths), 100s (15 mg and 30 mg), and UD 100s (15 mg and 30 mg).

4. The inactives are accurately listed in the DESCRIPTION section (pp 3012- 3014 v B 1.1).

6. The tablet descriptions are accurate as seen in the HOW SUPPLIED section (pp 3727, 3731, 3735 v B 1.2).

7. Storage Conditions:
NDA – Store at controlled room temperature 20°-25°C (68°-77°F).
ANDA – Store at controlled room temperature 15° - 30°C (59° - 86°F)[see USP].
USP – not USP

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

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

Date of Review: 7-4-02 Date of Submission: 6-6-02

Primary Reviewer: Adolph Vezza Date: 7/5/02

Team Leader: Lillie Golson /S/ Date: 7/5/02

/S/

cc: ANDA: 76-241
DUP/DIVISION FILE
HFD-613/AVezza/LGolson (no cc)
aev/7/4/02|V:\FIRMSAM\AMIDE\LTRS&REV\76241na2.l
Review

APPEARS THIS WAY
ON ORIGINAL

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

ANDA Number: **76-241** Date of Submission: **September 20, 2001**

Applicant's Name: **Amide Pharmaceutical, Inc.**

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

Labeling Deficiencies:

1. GENERAL COMMENT

   Add "(see USP)" to the end of the storage temperature recommendations on your container labels and unit dose carton and insert labeling.

2. CONTAINER 30s and 500s

   See GENERAL COMMENT above.

3. UNIT DOSE BLISTER

   "[redacted] rather than "Tablets"

4. UNIT DOSE CARTON

   a. See GENERAL COMMENT above.

   b. "outpatient" rather than " [redacted] (delete ' [redacted]

   c. 100 unit-dose tablets (10 X 10)

   d. Add the statement "PROTECT FROM LIGHT AND MOISTURE."

5. INSERT

   a. GENERAL COMMENTS

      i. Use "to" rather than a [redacted] when expressing a dosage range.

      ii. "*in vivo*" and "*in vitro*" (*italics*)

      iii. "Mirtazapine Tablets" need not be capitalized (i.e. "M" and "T") throughout the entire text.

   b. DESCRIPTION

      i. First paragraph - "molecular" rather than " [redacted]

ii. Inactive ingredients

A). "corn starch" (two words)

B). "hydroxypropyl methylcellulose (15 mg and 30 mg tablet)"

C). "lactose monohydrate"

D). "synthetic red iron oxide (30 mg tablet) and synthetic yellow iron oxide (15 mg tablet)

c. CLINICAL PHARMACOLOGY

i. Pharmacokinetics, last sentence - "mcg" rather than —

ii. Special Populations, Renal Insufficiency - "mL" rather than ' —

A). "... in administering mirtazapine ..."

B). "... DOSAGE AND ADMINISTRATION)."

d. PRECAUTIONS

General, Use in Patients with Concomitant Illness, last paragraph - "mL/min/1.73 m^2" (two instances)

e. ADVERSE REACTIONS

i. ECG Changes, first sentence - "placebo-controlled" (spelling)

ii. Other Adverse Events Observed During the Premarketing Evaluation of Mirtazapine

A). First paragraph, last sentence - "... first grouping similar types ..."

B). Musculoskeletal System - "arthrosis" rather than " —

f. DRUG ABUSE AND DEPENDENCE

Physical and Psychological Dependence, first sentence - "... for abuse, tolerance ..." (add comma)

g. DOSAGE AND ADMINISTRATION

Initial Treatment, penultimate sentence - "... adequately explored, patients not ..."

h. HOW SUPPLIED

"... and 100's (10 x 10) unit-dose tablets."

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

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

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

/S/

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 500s
Unit Dose Blister Labels:
Unit Dose Carton Labeling:
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
   no exclusivities
   The firm has filed a Paragraph IV certification to the patent.

3. Amide is the manufacturer (p 3166 v B 1.1).

4. The drug product will be made available in container sizes of 30s (CRC), 500s (non-CRC), and unit dose 100s (10 x 10). The RLD is available in container sizes of 30s (all three strengths), 100s (15 mg and 30 mg), and UD 100s (15 mg and 30 mg).

5. The inactives are accurately listed in the DESCRIPTION section except the firm has not stated that some of the ingredients are not present in all three strengths, also they spelled "corn starch" as all one word and they failed to state that the "lactose" is present as the monohydrate (pp 3012-3014 v B 1.1).

6. The tablet descriptions are accurate as seen in the HOW SUPPLIED section (pp 3727, 3731, 3735 v B 1.2).

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

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

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

Date of Review: 1-23-02 **Date of Submission:** 9-20-01

Primary Reviewer: Adolph Vezza /S/ **Date:** 1/24/02

Team Leader: Charlie Hoppes /S/ **Date:** 1/24/02

cc: ANDA: 76-241
DUP/DIVISION FILE
HFD-613/AVezza/CHoppes (no cc)
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Review

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

76-241

CHEMISTRY REVIEW(S)

1. CHEMISTRY REVIEW NO.1

2. ANDA # **76-241**

3. NAME AND ADDRESS OF APPLICANT
Amide Pharmaceutical, Inc.
101 East Main Street
Little Falls, NJ 7424

4. LEGAL BASIS FOR SUBMISSION
Generic version of Organon's Remeron® Tablets, 15 mg, 30 mg and 45 mg (NDA) #20-415).

Patent Certification and exclusivity statement are provided (Vol. 1.1, pp. 007-012B).

5. SUPPLEMENT(s) N/A -

6. PROPRIETARY NAME
Mirtazapine Tablets ~~15 mg~~

7. NONPROPRIETARY NAME
Mirtazapine Tablets

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

9. AMENDMENTS AND OTHER DATES:

Firm		**FDA**
Orig. Submission	~~10/5/01~~ 9/20/01 KS	Acknowledgement letter
		Bio review
Bio Amendment	1/07/01	Labeling review

10. (PROPOSED) INDICATION(S) FOR USE
Treatment of depression

11. Rx or OTC
℞

12. RELATED IND/NDA/DMF(s)
DMF ——
Others DMFs are identified in the container/closure element.

13. DOSAGE FORM
Tablet (Oral)

14. POTENCY
15 mg, 30 mg and 45 mg

15. CHEMICAL NAME AND STRUCTURE

16. RECORDS AND REPORTS None -

17. COMMENTS
a. Application contains CMC deficiencies
b. Labeling review pending
c. Bio review pending
d. Method validation submitted to the Philadelphia District Laboratory, dated 12/14/01
e. Establishment evaluation report pending

18. CONCLUSIONS AND RECOMMENDATIONS
NOT APPROVABLE

19. REVIEWER:
Raymond Brown

DATE COMPLETED:
January 18, 2002

APPEARS THIS WAY
ON ORIGINAL

Redacted 15

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

1. CHEMISTRY REVIEW NO. 2

2. ANDA # 76-241

3. NAME AND ADDRESS OF APPLICANT
Amide Pharmaceutical, Inc.
101 East Main Street
Little Falls, NJ 07424

4. LEGAL BASIS FOR SUBMISSION
Generic version of Organon's Remeron® Tablets, 15 mg, 30 mg and 45 mg (NDA) #20-415).

Patent Certification and exclusivity statement are provided (Vol. 1.1, pp. 007-012B).

5. SUPPLEMENT(s) N/A -

6. PROPRIETARY NAME
Mirtazapine Tablets

7. NONPROPRIETARY NAME
Mirtazapine Tablets

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

9. AMENDMENTS AND OTHER DATES:

Firm		FDA	
Orig. Submission	9/20/01		
New correspondence	11/9/01	Acknowledgement letter	11/14/01
		Bio review	11/27/01
		Bio deficiency letter	12/17/01
Bio Amendment	1/07/01		
New correspondence	1/14/02		
		Bio deficiency letter	1/30/01
		Deficiency letter	2/21/02
Amendment (minor)	6/6/02	T-call	8/19/02
Amendment (Chemistry)	8/20/02	T-call	1/14/03
Amendment (label)	8/26/02		
Amendment (label)	10/21/02		
Amendment (label)	11/08/02		
Amendment (CMC)	1/14/03		

10. (PROPOSED) INDICATION(S) FOR USE
Treatment of depression

11. Rx or OTC
℞

12. RELATED IND/NDA/DMF(s)
DMF
Others DMFs are identified in the container/closure element.

13. DOSAGE FORM
Tablet (Oral)

14. POTENCY
15 mg, 30 mg and 45 mg

15. CHEMICAL NAME AND STRUCTURE
Molecular weight: 265.36; $C_{17}H_{19}N_3$
Chemical name: 1,2,3,4,10,14b-hexahydro-2-methylpyrazino[2,1-a]pyrido[2,3-c]benzapine

16. RECORDS AND REPORTS None -

17. COMMENTS
a. ~~Application is approved pending labeling~~ review.
b. Labeling: Acceptable 12/4/02
c. Bio: Acceptable letter dated 1/31/02.
d. Methods validation submitted to the Philadelphia District Laboratory, dated 9/17/02
e. EER: Acceptable dated 1/24/02

18. CONCLUSIONS AND RECOMMENDATIONS
APPROVE

19. REVIEWER:
Radhika Rajagopalan

DATE COMPLETED:
September 17, 2002;
1/27/03
1/27/03

/S/

APPEARS THIS WAY
ON ORIGINAL

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

1. CHEMISTRY REVIEW NO. 3

2. ANDA # **76-241**

3. NAME AND ADDRESS OF APPLICANT
Amide Pharmaceutical, Inc.
101 East Main Street
Little Falls, NJ 07424

4. LEGAL BASIS FOR SUBMISSION
Generic version of Organon's Remeron® Tablets, 15 mg, 30 mg and 45 mg (NDA) #20-415).

Patent Certification and exclusivity statement are provided (Vol. 1.1, pp. 007-012B).

5. SUPPLEMENT(s) N/A -

6. PROPRIETARY NAME
Mirtazapine Tablets

7. NONPROPRIETARY NAME
Mirtazapine Tablets

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

9. AMENDMENTS AND OTHER DATES:

Firm		**FDA**	
Orig. Submission	9/20/01		
New correspondence	11/9/01	Acknowledgement letter	11/14/01
		Bio review	11/27/01
		Bio deficiency letter	12/17/01
Bio Amendment	1/07/01		
New correspondence	1/14/02		
		Bio deficiency letter	1/30/01
		Deficiency letter	2/21/02
Amendment (minor)	6/6/02	T-call	8/19/02
Amendment (Chemistry)	8/20/02	T-call	1/14/03
Amendment (label)	8/26/02	T-call	6/11/03
Amendment (label)	10/21/02		
Amendment (label)	11/08/02		
Amendment (CMC)	1/14/03		
Amendment (CMC)	6/10/03 np		
Amendment	5/28/03 np amd 7/11/03		

10. (PROPOSED) INDICATION(S) FOR USE
Treatment of depression

11. Rx or OTC
☐

12. RELATED IND/NDA/DMF(s)
DMF [redacted]
Others DMFs are identified in the container/closure element.

13. DOSAGE FORM
Tablet (Oral)

14. POTENCY
15 mg, 30 mg and 45 mg

15. CHEMICAL NAME AND STRUCTURE
Molecular weight: 265.36; $C_{17}H_{19}N_3$
Chemical name: 1,2,3,4,10,14b-hexahydro-2-methylpyrazino[2,1-a]pyrido[2,3-c]benzapine

16. RECORDS AND REPORTS None -

17. COMMENTS
a. Application is approved, based on acceptable labeling review.
b. Labeling: Acceptable 12/4/02
c. Bio: Acceptable letter dated 1/31/02.
d. EER: Acceptable dated 1/24/02
e. MV results are acceptable; comments from the lab were conveyed to the firm on 6/10/03 and a fax amendment was received, [redacted]
f. ANDA was issued a TA on 2/12/03.

18. CONCLUSIONS AND RECOMMENDATIONS
APPROVE

19. REVIEWER:
Radhika Rajagopalan

DATE COMPLETED:
6/16/03

6/18/03

Redacted 2

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

76-241

BIOEQUIVALENCE REVIEW(S)

BIOEQUIVALENCY DEFICIENCY

DEC 17 2001

ANDA: 76241

APPLICANT: Amide Pharmaceutical, Inc.

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

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

The dissolution testing was conducted in 0.01N HCL.

The dissolution testing should be conducted in 900 mL of 0.1N HCL at 37°C using USP Apparatus (II) at 50 rpm. Dissolution samples should be collected at 5 min, 10 min, 15 min and 20 min.

Sincerely yours,

/S/

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

Mirtazapine Tablets
15 mg, 30 mg and 45 mg
ANDA 76-241
Reviewer: James Chaney
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Amide Pharmaceutical, Inc.
Little Falls, NJ
Submission Date:
January 7, 2002

Amendment to Two Bioequivalence Studies, Dissolution Data and Waiver Requests Submitted on September 20, 2001

Submission History
The firm previously submitted (9/20/01) acceptable fasting and fed studies on the 15 mg strength, dissolution testing data on all strengths with waiver requests for the 30 mg and 45 mg strengths. The application was determined to be incomplete per the following dissolution deficiency (11/30/01 review by J. Chaney):

Deficiency
- The firm' sampling times were [redacted]. In view of the FDA specification of NLT [redacted] dissolved in 15 minutes and the rapid dissolution the following sampling times would be more appropriate: 5, 10, 15, and 20 minutes
- The firm used 0.01 N HCl as the medium. The FDA recommended medium is 0.1N HCl.
- The dissolution testing was unacceptable.

Firm's Response to Deficiency
The firm has submitted dissolution data obtained by the recommended FDA method, employing the recommended medium and sampling times.

Reviewer's Comment on Current Submission
- The results of the dissolution testing are satisfactory.
- The mean percent dissolved at 10 minutes (the second sampling time) is 88% or greater for all three strengths of the test products. Therefore, calculation of f_2 values was not pertinent.

RECOMMENDATIONS

1. The single-dose, fasting bioequivalence study and the single-dose post-prandial bioequivalence study conducted by Amide Pharmaceutical, Inc. on the test product, mirtazapine tablet 15 mg, lot RBR-955, comparing it with the reference product, Remeron® tablet 15 mg, 1019359054 manufactured by Organon have previously been found acceptable by the Division of Bioequivalence. The studies demonstrate that the test product, Amide Pharmaceutical's mirtazapine tablet 15 mg, is bioequivalent to the reference product, Remeron® tablet 15 mg, under fasting and non-fasting conditions.

2. The *in-vitro* dissolution testing conducted by Amide Pharmaceutical, Inc. on its mirtazapine tablets, 15 mg, 30 mg and 45 mg, has been found acceptable.

   The dissolution testing should be incorporated into firm's manufacturing controls and stability programs. The dissolution testing should be conducted in 900 mL of

0.1N HCl at 37°C using USP apparatus II (paddle) at 50 rpm. The test products should meet the following specifications:

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

3. The formulations for the 30 mg and 45 mg tablets are proportionally similar to the 15 mg tablet, which underwent acceptable bioequivalency testing. The waivers of *in vivo* bioequivalence study requirements for the 30 mg and 45 mg tablets of the test product are granted. The 30 mg and 45 mg test tablets are therefore deemed bioequivalent Remeron® 30 mg and 45 mg tablets manufactured by Organon.

4. From the bioequivalence point of view, the firm has met the requirements of *in vivo* bioequivalency and *in vitro* dissolution testing and the application is acceptable.

/S/

James E. Chaney, Ph.D.
Division of Bioequivalence
Review Branch I

RD INITIALED YCHuang
FT INITIALED YCHuang

/S/ Date 1/30/2002

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

/S/ Date 1/31/02

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TABLE 1. DISSOLUTION TESTING

Test Products: Mirtazapine Tablets
Dose strengths: 15 mg, 30 mg and 45 mg
Reference Products: Remeron® Tablets, 15 mg, 30 mg and 45 mg
Methodology Used By Firm:
USP XXIV apparatus: 2 (Paddle)
Medium: 0.1N HCl
Temperature: 37ºC
Volume: 900 mL
Rpm: 50
Detection: [illegible]

Results Of Dissolution Testing (% Dissolved In Minutes)

Sampling time (min)	Test product Mirtazapine Tablets 15 mg, Lot # RBR-955			Reference Product Remeron® Tablets 15 mg, Lot # 1019359054		
	Mean	Range	%CV	Mean	Range	%CV
5	73	[illegible]	14	65	[illegible]	18
10	93	[illegible]	3	93	[illegible]	7
15	96	[illegible]	2	98	[illegible]	2
20	97	[illegible]	2	99	[illegible]	1
30	98	[illegible]	1	100	[illegible]	1
Sampling time (min)	Test product Mirtazapine Tablets 30 mg, Lot # RBR-956			Reference Product Remeron® Tablets 30 mg, Lot # 849345469		
	Mean	Range	%CV	Mean	Range	%CV
5	60	[illegible]	25	43	[illegible]	32
10	90	[illegible]	5	82	[illegible]	12
15	93	[illegible]	4	95	[illegible]	6
20	95	[illegible]	3	99	[illegible]	2
30	97	[illegible]	2	100	[illegible]	1
Sampling time (min)	Test product Mirtazapine Tablets 45 mg, Lot # RBR-957			Reference Prc Remeron® Tablets 45 mg, Lot # 109298374		
	Mean	Range	%CV	Mean	Range	%CV
5	74	[illegible]	13	23	[illegible]	34
10	88	[illegible]	4	61	[illegible]	24
15	91	[illegible]	3	88	[illegible]	7
20	92	[illegible]	3	95	[illegible]	4
30	94	[illegible]	2	99	[illegible]	2

BIOEQUIVALENCY COMMENTS

ANDA: 76-241 APPLICANT: Amide Pharmaceutical, 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 II (Paddle) at 50 rpm. The test product should meet the following specifications:
>
> Not less than —(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,

/S/

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

CC: ANDA 76-241
ANDA DUPLICATE
DIVISION FILE
FIELD COPY
DRUG FILE

HFD-652/ J. Chaney /S/ 01/30/2002
HFD-652/ Y. Huang 1/30/2002
HFD-617/ K. Scardina 2/1/02
HFD-650/ D. Conner 1/31/02

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BIOEQUIVALENCY – ACCEPTABLE

Submission date: January 7, 2002

STUDY AMENDMENT (STA) 01

Strengths: 15 mg, 30 mg and 45 mg
Outcome: AC

NOTE:

AC - Acceptable
NC - No Action
UN - Unacceptable
IC - Incomplete

Outcome Decision: Incomplete

WINBIO COMMENT:

The firm has met the requirements of *in vivo* bioequivalency and *in vitro* dissolution testing and the application is acceptable.

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA # 76-241 SPONSOR : Amide Pharmaceutical, Inc.
DRUG AND DOSAGE FORM: Mirtazapine Tablets
STRENGTH(S): 15 mg, 30 mg, 45 mg
TYPES OF STUDIES: Fasting, postprandial and dissolution
CINICAL STUDY SITE: [redacted]

ANALYTICAL SITES: [redacted]

STUDY SUMMARY: Fasting and postprandial studies are acceptable

DISSOLUTION: Acceptable.

DSI INSPECTION STATUS

Inspection needed: No	Inspection status:	Inspection results:
First Generic No New facility No For cause _____ Other _____	Inspection requested: (date) Inspection completed: (date)	

PRIMARY REVIEWER: James Chaney BRANCH: I
INITIAL: _____ DATE: 1/30/02

TEAM LEADER: Yih-Chain Huang BRANCH: I
INITIAL: _____ DATE: 1/30/2002

DIRECTOR, DIVISION OF BIOEQUIVALENCE: DALE P. CONNER, Pharm.D.
INITIAL : _____ DATE : 1/31/02

Mirtazapine Tablets
15 mg, 30 mg and 45 mg
ANDA 76-241
Reviewer: James Chaney
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Amide Pharmaceutical, Inc.
Little Falls, NJ
Submission Date:
September 20, 2001

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

I. Introduction

Indication: Mirtazapine is a noradrenergic and specific serotonergic antidepressant indicated for the treatment of depression.
Type of Submission: Original
Contents of Submission:

- Fasting and non-fasting studies on the 15 mg tablet.
- Dissolution data on 15 mg, 30 mg and 45 mg tablets.
- Waiver requests on the 30 mg and 45 mg strengths.

RLD: Remeron® (Mirtazapine) tablets are available in three strengths: 15 mg, 30 mg and 45 mg. The Orange Book (Electronic 2001) lists Remeron® 15 mg tablet manufactured by Organon as the reference listed drug (NDA 20415, July 14, 1996). Mirtazapine tablets are also available as orally disintegrating tablets, Remeron® SolTab™ 15 mg, 30 mg and 45 mg strengths (NDA 21-208) manufactured by Organon.
Recommended Dose: The recommended starting dose for Remeron® (mirtazapine) Tablets is 15 mg/day, administered in a single dose. In the controlled clinical trials establishing the antidepressant efficacy of Remeron® the effective dose range was generally 15-45 mg/day.
First Generic: No
Financial Disclosure: Form FDA 3454 was submitted. The firm has no conflict of interest with the investigators.
Bioequivalence Requirements for Mirtazapine
The current BE requirements for Mirtazapine are for the conduct of a single dose fasting and a single dose nonfasting study on the 15 mg tablet with analysis of only the parent drug. Currently, the Division of Bioequivalence recommends the following for bioequivalence studies on mirtazapine:

- Conduct both fasting and non-fasting studies to establish bioequivalence.
- Measurement of plasma racemate levels of mirtazapine only for bioequivalence assessment.
- Quantitation of the metabolites of mirtazapine for the bioequivalence studies is not recommended.

II. Background

Pharmacokinetics:
After an oral dose of mirtazapine, the Tmax is reached in about 2 hours. It undergoes gut wall and liver first-pass metabolism. The elimination half-life is about 20-40 hours. Mirtazapine displays linear kinetics over the dosing range of 15-80 mg/day.
Food Effect:
Food has little effect on plasma mirtazapine levels, but does delay Tmax.
Metabolites:
The major metabolites of mirtazapine are not very active, and are of little clinical importance.

As indicated in the NDA 20-415 review, only N-demethyl mirtazapine was found to be pharmacologically active and at very low levels in human plasma. Therefore the quantitation of metabolites of mirtazapine is not requested for the BE studies.

III. Single-dose Fasting Bioequivalence Study on the 15 mg Strength

Study Information

STUDY FACILITY INFORMATION

Clinical Facility:	[redacted]
Medical Director:	[redacted]
Scientific Director:	[redacted]
Clinical Study Dates:	04/14/01 to 05/09/01
Analytical Facility	[redacted]
Principal Investigator:	[redacted]
Analytical Study Dates:	05/10/01 to 05/23/01
Storage Period:	The maximum time samples were stored frozen from the first day of collection (4/15/01) to the last day of analysis (5/23/01) was 38 days. The validated frozen plasma stability is 171 days.

TREATMENT INFORMATION

Treatment ID:	A	B
Test or Reference:	T	R
Product Name:	Mirtazapine	Remeron®
Manufacturer:	Amide Pharmaceutical, Inc.	Organon, Inc.
Manufacture Date:	Mar-01	N/A
Expiration Date:	NA	Mar-03
ANDA Batch Size:	[redacted]	N/A
Full Batch Size:	[redacted]	N/A
Batch/Lot Number:	RBR-955	1019359054
Potency:	100.0%	100.2%
Content Uniformity:	100.9 (98.9-102.8) 1.2%CV	101.0 (99.4-102.9) 1.5%CV
Strength:	15 mg	15 mg
Dosage Form:	Tablet	Tablet
Dose Administered:	15 mg	15 mg
Study Condition:	Fasting	Fasting
Length of Fasting:	Overnight	Overnight

RANDOMIZATION		DESIGN	
Randomized:	Y	**Design Type:**	Crossover
No. of Sequences:	2	**Replicated Treatment Design:**	N
No. of Periods:	2	**Balanced:**	Y
No. of Treatments:	2	**Washout Period:**	21 days

AB: 2, 3, 5, 6, 9, 10, 12, 14, 17, 19, 20, 23, 24, 26, 27, 29, 33, 35, 37, 39, 41, 42, 45
BA 1, 4, 7, 8, 11, 13, 15, 16, 18, 21, 22, 25, 28, 30, 31, 32, 34, 36, 38, 40, 43, 44, 46

Demographics of the 46 Enrolled Subjects

Age (yrs): 32.5±8.0(19-44)

	Age Group	
	< 18 yrs	0
	18-39 yrs	34 (74%)
	40-64 yrs	12 (26%)
	65-75 yrs	0
	> 75 yrs	0
Sex	Female	0
	Male	46 (100%)
Race	Asian	0
	Black	1 (2%)
	Caucasian	44 (96%)
	Hispanic	0
	Other (Mulatto)	1 (2%)

Weight (lbs): 164.6±13.8 (138-193)

Height (in): 68.9±2.0(64.6-74.0)

DOSING		SUBJECTS	
Single or Multiple Dose:	Single	**IRB Approval:**	Y
Steady State:	N	**Informed Consent Obtained:**	Y
Volume of Liquid Intake:	240 mL	**No. of Subjects Enrolled:**	46
Route of Administration:	Oral	**No. of Subjects Completing:**	45
Dosing Interval:	N/A	**No. of Subjects Plasma Analyzed:**	44*
Number of Doses:	N/A	**No. of Dropouts:**	1
Loading Dose:	N/A	**Sex(es) Included:**	Male
Steady State Dose Time:	N/A	**Healthy Volunteers Only:**	Y
Length of Infusion:	N/A	**No. of Adverse Events:**	115

*per protocol

Dietary Restrictions: No alcohol- or xanthine-containing foods/beverages 24hrs pre-dose and throughout the period of sample collection. No grapefruit-containing beverages/foods for 10 days pre-dose and throughout the entire study.

Activity Restrictions: Subject were seated in bed and remained in bed for the first 4hrs post-dose. In case of adverse events subjects were placed in appropriate position or permitted to lie down on their right side. No strenuous activity at any time during the study.

Drug Restrictions: No medication (including over-the-counter products but not including vitamins for non-therapeutic indications)) for the 7 days preceding the study.

Blood Sampling: Pre-dose and at the following times post-dose (7 mL): 0.25, 0.5, 0.75, 1, 1.25, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 16, 24, 36, 48, 72 and 96 hours

Study Results

1) Clinical

Adverse Events:

The adverse reactions included burning eyes, bruise below venipuncture site, burning sensation in upper abdominal area, difficulty in concentrating, disorientation, dizziness, dry mouth, dry throat, feels hot, sleepiness, headache, fast heart beat, lower back pain, muscle pain in right shoulder, nausea, numbness, pain in legs, pain in thighs, pain in muscles all over the body, pain in the scalp area, rash lower right back side, rash on lower abdomen, sore throat, drunk feeling and vomiting.

A total of 121 adverse events (50 following test product and 71 following reference product) were experienced by 43 subjects during the study. Of these events, 40 (20 following test product and 20 following reference product) were judged to have a definite association with the study drug. Forty-five events (23 following test product and 22 following reference product) were judged to have a probable association with the study drug. Twenty-two (3 following test product and 19 following reference product) were judged to have a possible association with the study drug. Eight (3 following test product and 5 following reference product) were judged to have a remote association with the study drug and 6 were judged to be unrelated to the study drug. The adverse events were mild or moderate in severity.

Protocol Deviations:

Vital signs were measured while subjects were in a supine position (reason not recorded):

- Subject No. 25's 2-hour vital signs in Period 1.
- Subject No. 36's 4-hour vital signs in Period 1 and 2-hour vital signs in Period 2.
- Subject No. 46's 4-hour vital signs in Period 1.

Subject No. 25 consumed a cup of coffee (8 ounces) 1.9 days post-dose in Period 1.

Post-dose blood samples were taken within 2 minutes of their scheduled times except as otherwise reported.

None of the above deviations would compromise the study integrity.

Dropouts:

SUBJECT NO.:	46
REASON:	Adverse events
PERIOD:	1
REPLACEMENT:	N

2) Analytical (Not to be Released Under FOI)

Description of Analytical Method Validation

Analyte: [redacted]
Assay Method: [redacted]
Matrix: [redacted]
Internal Standard: [redacted]

Redacted _____

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DURING STUDY ASSAY VALIDATION FOR FASTING STUDY

[redacted]

to anomalous PK values (see Comments On Fasting Study).

Comments: The analytical method is acceptable.

3) Pharmacokinetics:

Mean Plasma Concentrations:	Table 1, Figure 1	
Pharmacokinetic Parameters:	Tables 2, 3 and 3a	
90% Confidence Intervals:	LAUC0-t	99.1-107.3%
	LAUC0-inf	99.1-106.8%
	LCmax	102.6-118.3%
Arith. Mean AUCT/AUCI Ratios:	Test	0.93 (0.86-0.97), 2%CV
	Ref	0.93 (0.87-0.97), 2%CV
Arith. Mean T/R Ratios:	AUC0-t	1.04 (0.75-1.36), 15%CV
	AUC0-inf	1.04 (0.74-1.33), 14%CV
	Cmax	1.15 (0.57-1.94), 29%CV
Root MSE:	LAUC0-t	0.111153
	LAUC0-inf	0.104450
	LCmax	0.197834

Comments On Fasting Study:

1. The reviewer recalculated pharmacokinetic parameters and 90% confidence intervals. The reported values are in satisfactory agreement with those obtained by the reviewer.

2. There was no observation of a first measurable drug concentration as Cmax.

3. Three subjects (subjects 2, 6 and 22 of period 1) had pre-dose drug concentrations greater than 5% of their Cmax values. These three subjects were deleted from the data set per the BA/BE General Guidance.

4. Of the 1848 samples only 19 (1%) were reassayed by the firm due to anomalous PK values. Upon re-assay all 19 samples gave results which were reported and all 19 reported values were different from the original analysis values.

5. Following deletion of the above three subjects with significant pre-dose values there remained 16 of 1722 samples (1%) which the firm had reassayed to give values different from the original analysis. The reviewer substituted the original analytical values into the data set, statistically reanalyzed the data and found that the log-transformed 90% confidence intervals for LAUCT, LAUCI and Cmax changed only slightly and remained within the range of 80-125%.

6. The fasting study is acceptable.

IV. Single-dose Post-Prandial Bioequivalence Study on the 15 mg Strength

A. Study Information

STUDY FACILITY INFORMATION

Clinical Facility: [redacted]
Medical Director: [redacted]
Scientific Director: [redacted]
Clinical Study Dates: 06/02/01 to 06/27/01
Analytical Facility [redacted]
Principal Investigator: [redacted]
Analytical Study Dates: 06/29/01 to 07/12/01
Storage Period: The maximum time samples were stored frozen from the first day of collection (6/3/01) to the last day of analysis (7/12/01) was 39 days. The validated frozen plasma stability is 171 days.

TREATMENT INFORMATION

Treatment ID:	A	B
Test or Reference:	T	R
Product Name:	Mirtazapine	Remeron®
Manufacturer:	Amide Pharmaceutical, Inc.	Organon, Inc.
Manufacture Date:	3/1/01	N/A
Expiration Date:	N/A	N/A
Batch/Lot Number:	RBR-955	1019359054
Strength:	15 mg	15 mg
Dosage Form:	tablet	Tablet
Dose Administered:	15 mg	15 mg
Study Condition:	Fed	Fed
Length of Fasting:	overnight	Overnight
Standardized Breakfast:	Y	Y
Standardized Lunch:	Y	Y
Standardized Dinner:	Y	Y

RANDOMIZATION		DESIGN	
Randomized:	Y	**Design Type:**	Crossover
No. of Sequences:	2	**Replicated Treatment Design:**	N
No. of Periods:	2	**Balanced:**	N
No. of Treatments:	2	**Washout Period:**	21 days

AB: 3, 5, 6, 7, 9, 11, 12, 16, 17
BA: 1, 2, 4, 8, 10, 13, 14, 15, 18

Demographics of the 18 Enrolled Subjects

Age (yrs): 30.6±5.2(22-40)

	Age Group	
	< 18 yrs	0
	18-39 yrs	17 (94%)
	40-64 yrs	1 (6%)
	65-75 yrs	0
	> 75 yrs	0
Sex	Female	0
	Male	18 (100%)
Race	Asian	0
	Black	1 (6%)
	Caucasian	17 (94%)
	Hispanic	0
	Other (Mulatto)	1 (2%)

Weight (lbs): 163.8±16.6 (133-195)
Height (in): 68.2±3.0(63.0-74.4)

DOSING		SUBJECTS	
Single or Multiple Dose:	single	**IRB Approval:**	Y
Steady State:	N	**Informed Consent Obtained:**	Y
Volume of Liquid Intake:	240 mL	**No. of Subjects Enrolled:**	18
Route of Administration:	oral	**No. of Subjects Completing:**	16
Dosing Interval:	hr	**No. of Subjects Plasma Analy**	16
Number of Doses:	N/A	**No. of Dropouts:**	2
Loading Dose:	mg	**Sex(es) Included:**	male
Steady State Dose Time:	N/A	**Healthy Volunteers Only:**	Y
Length of Infusion:	N/A	**No. of Adverse Events:**	38

Dietary Restrictions: No alcohol- or xanthine-containing foods/beverages 24hrs pre-dose & throughout period of sample collection. No grapefruit-containing foods/beverages 10 days pre-dose and throughout the entire study.

Activity Restrictions: Subjects were seated in bed and remained in bed for the first 4hrs post-dose. In case of adverse events subjects were placed in an appropriate position or were permitted to lie down on their right side. No strenuous activity at any time during the study.

Drug Restrictions: No medication (including over-the-counter products, but not including vitamins taken for non-therapeutic indications) for the 7 days preceding the study.

Blood Sampling Times: 0, 0.5, 0.75, 1, 1.25, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 12, 16, 24, 36, 48, 72, 96,

Study Results

1) Clinical
Adverse Events:
The adverse reactions included abdominal pain, burning sensation in upper abdominal area, convulsions, dizziness, fainting, drowsiness, sleepiness, itchiness, muscle pain from left hip to front of left knee, numbness, pain in the right shoulder, redness, right chest pain, bloated feeling after eating and tiredness.

A total of 39 adverse events (18 following test product and 21 following reference product) were experienced by 15 subjects during the study. Of these events, 28 (11 following test product and 17 following reference product) were judged to have a definite association with the study drug Three (all following test product) were judged to have a probable association with the study drug. Seven (3 following test product and 4 following reference product) were judged to have a possible association with the study drug. These events were mild or moderate in severity.

Protocol Deviations:
Post-dose blood samples were taken within 2 minutes of their scheduled times except as otherwise reported.

None of the above deviations would compromise the study integrity.

Dropouts:

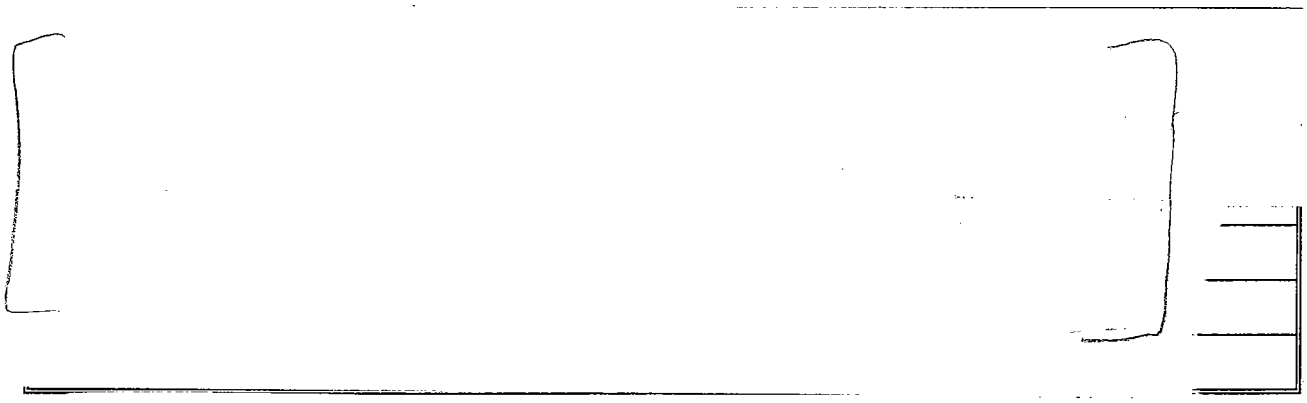
SUBJECT NO.:	13	18
REASON:	Adverse events	Positive drug screen (cannabinoids)
PERIOD:	1	2
REPLACEMENT:	N	N

Of the 18 subjects who began this study, 16 completed both phases. Subject No. 13 was withdrawn from the study due to adverse events after his 24-hour blood draw in Period 1 and Subject No. 18 was withdrawn due to a positive drug screen for cannabinoids prior to dosing in Period 2.

2) Analytical (Not to be Released Under FOI)

Within-Study Bioanalytical Method Validation
Analytical method and Pre-Study Assay Validation are same as for fasting study.

DURING STUDY ASSAY VALIDATION



Comments:
The analytical method is acceptable.

3) Pharmacokinetics:

Mean Plasma Concentrations:	Table 4, Figure 2	
Pharmacokinetic Parameters:	Tables 5 and 6	
Arith. Mean AUCT/AUCI Ratios:	Test	0.94 (0.89-0.97), 2%CV
	Reference	0.92 (0.85-0.96), 3%CV
Arith. Mean T/R Ratios:	AUC0-t	1.06 (0.84-1.34), 12%CV
	AUC0-inf	1.02 (0.85-1.20), 12%CV
	Cmax	0.95 (0.58-1.27), 21%CV

Comments on Nonfasting Study:

- There were no measurable drug concentrations at 0 hr. There was no observation of first measurable drug concentration as Cmax.
- The point estimates for AUCt, AUCi, Cmax are within the acceptable limits of 80-125%.
- The firm reported that 90% confidence intervals for log transformed AUC0-t, AUC0-inf, and Cmax are within acceptable limits of 80-125%, but they are not currently required by DBE for food studies.
- Pharmacokinetic parameters calculated by the reviewer are in satisfactory agreement with firm's calculations.

Conclusion: The nonfasting bioequivalence study is acceptable.

IV. Formulation

- Formulation information is provided in Table 7.
- All inactive ingredients in the formulation were present at or below the levels cited in the FDA Inactive Ingredient Guide (1996) for approved drug products.
- The formulation for the 30 mg and 45 mg mirtazapine tablets are proportionally similar to that of the 15 mg strength per definition 1 in BA/BE Guidance for Industry for Orally Administered Drug Products issued on October 27, 2000.

V. Dissolution

A. Dissolution Method Used by Firm

No. Units Tested: 12 tablets
USP XXIV apparatus: 2 (Paddle)
Medium: 0.01N HCl
Temperature: 37°C
Volume: 900 mL
Rpm: 50
Sampling Times: [redacted]
Tolerance: NLT [redacted] (Q) in 30 min

B. Results

Dissolution data are presented in Table 8.
The dissolution testing was conducted by Amide Pharmaceutical, Inc. Greater than [redacted] of the drug was dissolved at the second sampling time for all strengths of the test and reference products.

C. Comments:

- The firm' sampling times were [redacted]. In view of the FDA specification of NLT [redacted] dissolved in 15 minutes and the rapid dissolution the following sampling times would be more appropriate: 5, 10, 15, and 20 minutes
- The FDA recommended medium is 0.1N HCl. The firm used 0.01 N HCl as the medium.
- The dissolution testing is unacceptable.

VI. RECOMMENDATIONS:

1. The single-dose, fasting bioequivalence study and the single-dose post-prandial bioequivalence study conducted by Amide Pharmaceutical, Inc. on the test product, mirtazapine tablet 15 mg, lot RBR-955, comparing it with the reference product, Remeron® tablet 15 mg, 1019359054 manufactured by Organon have been found acceptable by the Division of Bioequivalence. The studies demonstrate that the test product, Amide Pharmaceutical's mirtazapine tablet 15 mg, is bioequivalent to the reference product, Remeron® tablet 15 mg, under fasting and non-fasting conditions.

2. The in-vitro dissolution testing conducted by Amide Pharmaceutical, Inc. on its mirtazapine tablets, 15 mg, 30 mg and 45 mg, is not acceptable.

   The dissolution testing should be conducted in 900 ml of 0.1N HCL at 37°C using USP apparatus II (paddle) at 50 rpm with sampling at 5, 10, 15, and 20 minutes.

3. The formulations for the 45 mg and 30 mg tablets are proportionally similar to the 15 mg tablet, which underwent bioequivalency testing. The waivers of *in vivo* bioequivalence study requirements for the 45 mg and 30 mg tablets of the test product are pending acceptable dissolution testing.

4. From the bioequivalence point of view, the application is incomplete per the dissolution deficiency.

/S/

James E. Chaney, Ph.D.
Division of Bioequivalence
Review Branch I

RD INITIALED YCHuang
FT INITIALED YCHuang /S/ Date 11/28/2001

Concur: /S/ Date 11/30/01
Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence

JEC/112701
V:\FIRMSAM\AMIDE\LTRS&REV\76241sdw901.doc

Mirtazapine Tablets, 15 mg, 30 mg and 45 mg, Amide Pharmaceutical, Inc., ANDA 76-241

APPEARS THIS WAY
ON ORIGINAL

TABLE 1. ARITHMETIC MEAN PLASMA MIRTAZAPINE CONCENTRATIONS [NG/ML] (CV%) VERSUS TIME IN 44 SUBJECTS UNDER FASTING CONDITIONS

TIME (HR)	TEST TREATMENT A		REFERENCE TREATMENT B		RATIO (A/B)%
0	0.0000	(0.0)	0.0000	(0.0)	N/AP
0.25	0.0000	(0.0)	0.0000	(0.0)	N/AP
0.5	2.9461	(157.2)	1.6020	(146.6)	183.9
0.75	14.9724	(83.1)	10.4571	(76.5)	143.2
1	26.7077	(44.6)	23.2498	(51.0)	114.9
1.25	31.9340	(39.2)	28.4770	(37.1)	112.1
1.5	31.9516	(29.4)	29.7561	(26.2)	107.4
2	29.1430	(25.4)	28.8887	(23.4)	100.9
2.5	26.7871	(26.8)	26.1111	(23.3)	102.6
3	24.4176	(25.3)	23.6104	(20.7)	103.4
4	21.0593	(27.3)	20.5867	(22.6)	102.3
6	14.5558	(28.0)	13.9165	(21.7)	104.6
8	11.1599	(27.2)	10.8509	(23.4)	102.8
10	8.0926	(28.4)	7.7370	(22.8)	104.6
12	6.6998	(30.9)	6.3186	(23.9)	106.0
16	4.9299	(31.1)	4.7785	(24.5)	103.2
24	3.3314	(34.2)	3.2640	(27.3)	102.1
36	2.0486	(45.2)	1.9775	(33.2)	103.6
48	1.3096	(49.3)	1.2658	(45.1)	103.5
72	0.5176	(101.8)	0.4647	(103.8)	111.4
96	0.1416	(214.5)	0.1703	(183.7)	83.1

FIGURE 1B

PLASMA MIRTAZAPINE CONCENTRATIONS (NG/ML) VERSUS TIME
SINGLE-DOSE FASTING STUDY #003268
(LINEAR PLOT)

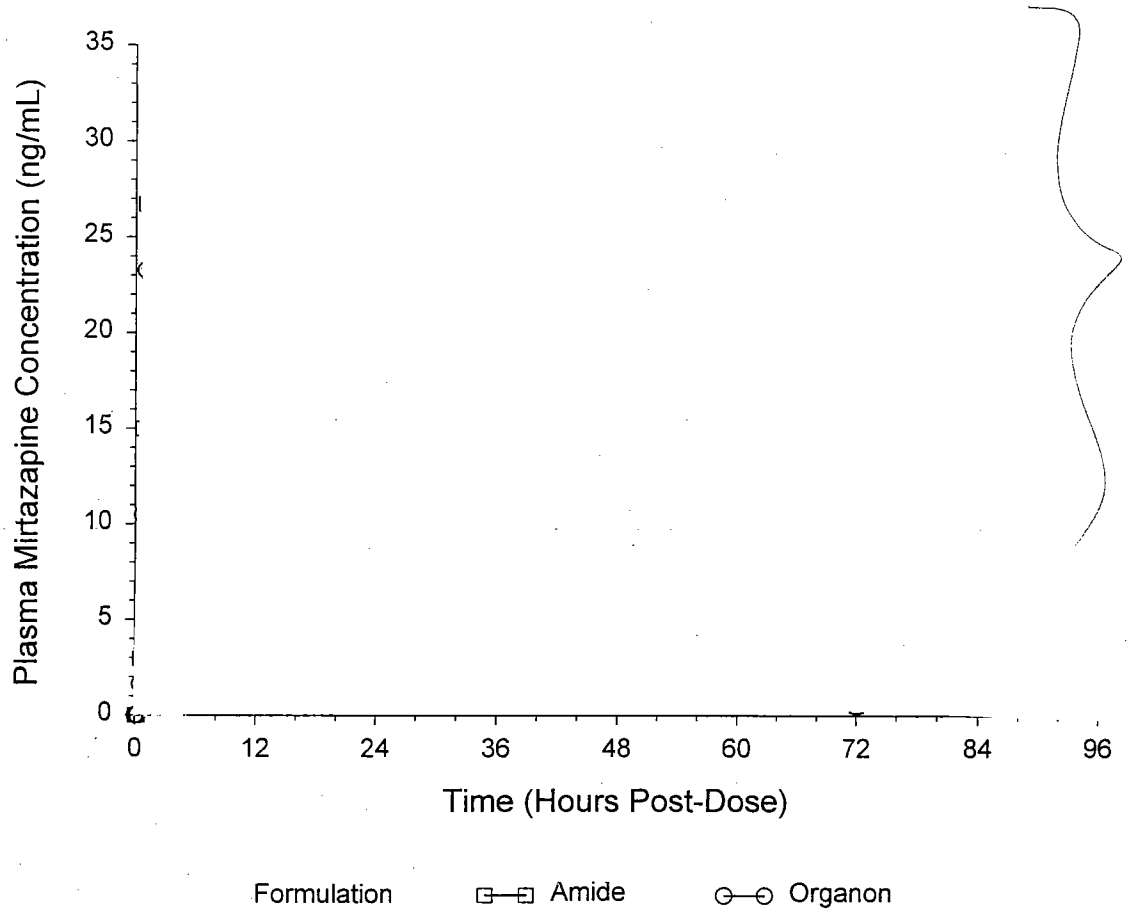


TABLE 2. MIRTAZAPINE ARITHMETIC MEANS (CV%) OF PHARMACOKINETIC PARAMETERS IN 44 SUBJECTS UNDER FASTING CONDITIONS

PK PARAMET	N	TEST TREATMENT A		N	REFERENCE TREATMENT B		RATIO (A/B)%
AUC(0-t) [ng•hr/mL]	44	314.6	(32.2)	44	301.2	(26.9)	104.4
AUC(0-inf) [ng•hr/mL]	44	336.3	(31.7)	44	323.3	(26.8)	104.0
Cmax [ng/mL]	44	36.9160	(30.0)	44	33.3417	(26.7)	110.7
Tmax [hr]	44	1.551	(37.7)	44	1.648	(31.9)	94.1
kel [1/hr]	44	0.04002	(41.1)	44	0.03886	(36.7)	103.0
Half-life [hr]	44	19.851	(36.0)	44	20.291	(36.1)	97.8

TABLE 3. FASTING IN VIVO BIOEQUIVALENCE STUDY, GEOMETRIC LSMEANS AND 90% CONFIDENCE INTERVALS FOR PHARMACOKINETIC PARAMETERS, N=44

PK PARAMETER	TEST TREATMENT A	REFERENCE TREATMENT B	RATIO (A/B)%	90% C.I.
AUC(T) [ng.hr/mL]	299.9	290.9	103.1	99.1-107.3
AUC(I) [ng.hr/mL]	321.3	312.4	102.8	99.1-106.8
Cmax [ng/mL]	35.44	32.16	110.2	102.6-118.3

TABLE 3a. FASTING IN VIVO BIOEQUIVALENCE STUDY, GEOMETRIC LSMEANS AND 90% CONFIDENCE INTERVALS FOR PHARMACOKINETIC PARAMETERS UPON REVIEWER'S STATISTICAL ANALYSIS FOLLOWING DELETION OF 3 SUBJECTS AND SETTING REASSAYED VALUES TO THE ORIGINAL VALUES, N=41.

PK PARAMETER	TEST TREATMENT A	REFERENCE TREATMENT B	RATIO (A/B)%	90% C.I.
AUC(T) [ng.hr/mL]	302.4	295.2	102	97.8-107.3
AUC(I) [ng.hr/mL]	308.5	301.4	102	97.7-107.2
Cmax [ng/mL]	35.19	32.31	109	101.3-117.1

TABLE 4. ARITHMETIC MEAN MIRTAZAPINE PLASMA CONCENTRATIONS [NG/ML] (CV%) VERSUS TIME IN 16 SUBJECTS - FED

TIME (HR)	TEST TREATMENT A		REFERENCE TREATMENT B		RATIO (A/B)%
0	0.0000	(0.0)	0.0000	(0.0)	N/AP
0.5	0.6301	(330.1)	1.0011	(280.5)	62.9
0.75	2.4330	(164.9)	4.0016	(215.1)	60.8
1	7.0014	(120.2)	8.1388	(157.2)	86.0
1.25	10.5448	(80.4)	9.8897	(118.7)	106.6
1.5	15.8446	(66.3)	13.8343	(98.3)	114.5
2	21.6400	(44.7)	17.3025	(62.4)	125.1
2.5	23.3817	(39.5)	21.0444	(39.5)	111.1
3	24.3961	(32.2)	21.2649	(30.3)	114.7
3.5	23.0719	(32.2)	22.8413	(28.9)	101.0
4	23.9490	(27.9)	24.0447	(28.2)	99.6
5	21.8851	(27.0)	24.6139	(41.5)	88.9
6	16.9714	(28.5)	18.3384	(32.4)	92.5
8	12.8161	(29.3)	13.1761	(33.6)	97.3
10	9.4228	(25.9)	9.7063	(32.8)	97.1
12	8.1146	(26.7)	7.8733	(31.1)	103.1
16	5.3173	(31.4)	5.3947	(30.8)	98.6
24	3.6640	(27.7)	3.7469	(31.9)	97.8
36	3.2098	(89.3)	2.3169	(36.7)	138.5
48	1.6085	(36.2)	1.4969	(43.0)	107.5
72	0.6950	(64.6)	0.5897	(106.7)	117.9
96	0.1987	(155.7)	0.1973	(186.0)	100.7

FIGURE 2

PLASMA MIRTAZAPINE CONCENTRATIONS (NG/ML) VERSUS TIME
SINGLE-DOSE FED STUDY #003269
(LINEAR PLOT)

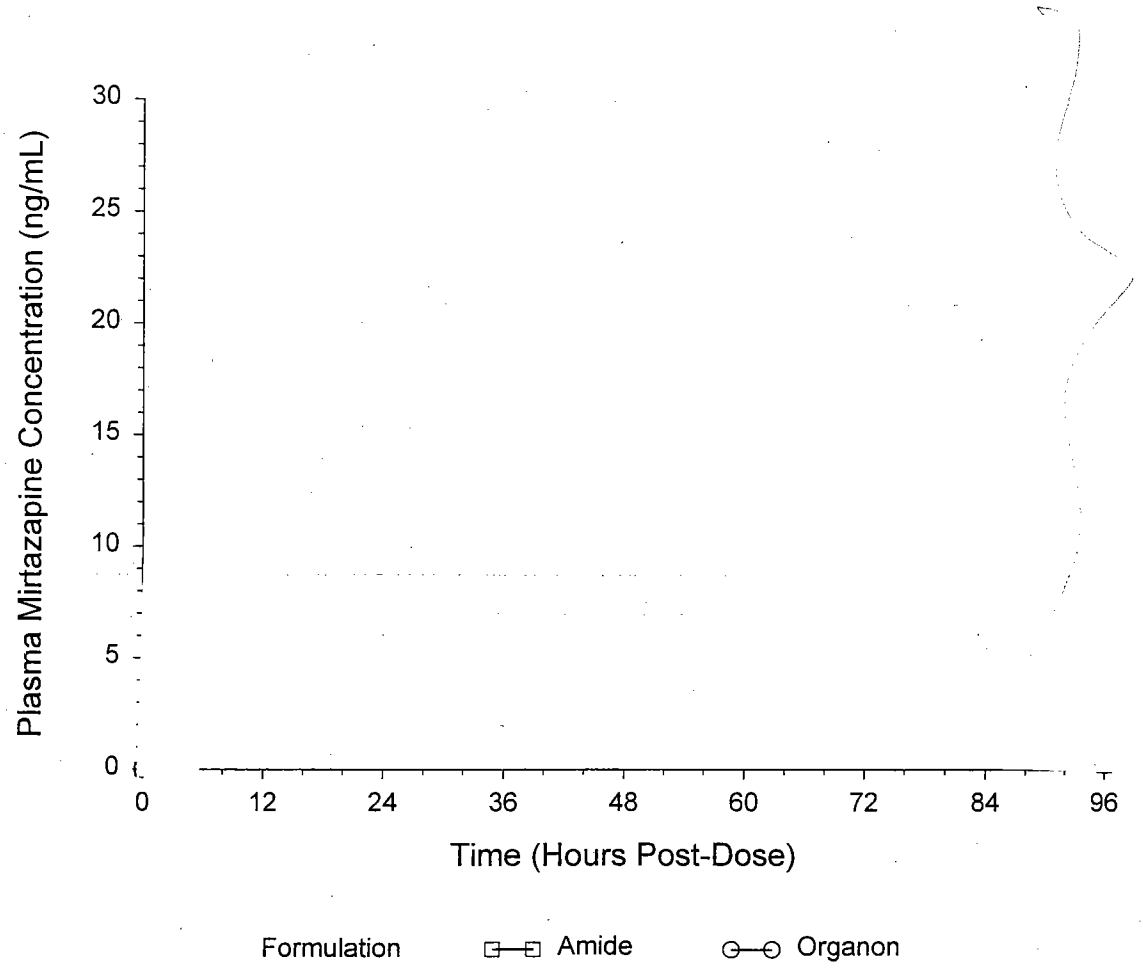


TABLE 5. MIRTAZAPINE ARITHMETIC MEANS (CV%) OF PHARMACOKINETIC PARAMETERS IN 16 SUBJECTS UNDER FED CONDITIONS

PK PARAMET	N	TEST TREATMENT A		N	REFERENCE TREATMENT B		RATIO (A/B)%
AUC(0-t) [ng•hr/mL]	16	340.7	(27.8)	16	323.9	(28.7)	105.2
AUC(0-inf) [ng•hr/mL]	15	353.6	(26.9)	16	350.4	(28.0)	100.9
Cmax [ng/mL]	16	29.0265	(24.6)	16	30.9735	(24.7)	93.7
Tmax [hr]	16	3.313	(36.9)	16	3.281	(44.8)	101.0
kel [1/hr]	15	0.03488	(23.8)	16	0.03710	(29.6)	94.0
Half-life [hr]	15	20.90	(22.8)	16	20.24	(28.8)	103.3

TABLE 6. POST-PRANDIAL IN VIVO BIOEQUIVALENCE STUDY, GEOMETRIC MEAN LEAST-SQUARES MEAN PK VALUES

PK PARAMETER	N	FED TEST (A)	N	FED REFERENCE (B)	RATIO (A/B)%
AUC(T) [ng.hr/mL]	16	328.8	16	314.2	104.7
AUC(I) [ng.hr/mL]	15	343.5	16	340.4	100.9
Cmax [ng/mL]	16	28.21	16	30.40	92.8

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ON ORIGINAL

formulation
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TABLE 8. DISSOLUTION TESTING

Test Products: Mirtazapine Tablets
Dose strengths: 15 mg, 30 mg and 45 mg
Reference Products: Remeron® Tablets, 15 mg, 30 mg and 45 mg
Methodology Used By Firm:
USP XXIV apparatus: 2 (Paddle)
Medium: 0.01N HCl
Temperature: 37°C
Volume: 900 mL
Rpm: 50
Detection: [redacted]

Results Of Dissolution Testing (% Dissolved In Minutes)

Sampling time (min)	Test product Mirtazapine Tablets 15 mg, Lot # RBR-955			Reference Product Remeron® Tablets 15 mg, Lot # 1019359054		
	Mean	Range	%CV	Mean	Range	%CV
[redacted]	92.8	[redacted]	3	77.7	[redacted]	5
[redacted]	96.3	[redacted]	2	97.3	[redacted]	3
[redacted]	97.4	[redacted]	2	101.9	[redacted]	2
[redacted]	98.9	[redacted]	1	101.6	[redacted]	1
Sampling time (min)	Test produc Mirtazapine Tablets 30 mg, Lot # RBR-956			Reference Product Remeron® Tablets 30 mg, Lot # 849345469		
	Mean	Range	%CV	Mean	Range	%CV
[redacted]	92.8		2	70.3	[redacted]	13
[redacted]	96.6		2	94.9	[redacted]	4
[redacted]	99.2		1	100.3	[redacted]	1
[redacted]	101.0		2	101.6	[redacted]	1
Sampling time (min)	Test product Mirtazapine Tablets 45 mg, Lot # RBR-957			Reference Product Remeron® Tablets 45 mg, Lot # 109298374		
	Mean	Range	%CV	Mean	Range	%CV
[redacted]	91.7	[redacted]	2	60.7	[redacted]	15
[redacted]	94.1	[redacted]	2	94.6	[redacted]	5
[redacted]	96.9	[redacted]	1	100.9	[redacted]	2
[redacted]	98.6	[redacted]	1	103.2	[redacted]	2

BIOEQUIVALENCY DEFICIENCY

ANDA: 76241 APPLICANT: Amide Pharmaceutical, Inc.

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

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

The dissolution testing was conducted in 0.01N HCL.

The dissolution testing should be conducted in 900 mL of 0.1N HCL at 37°C using USP Apparatus (II) at 50 rpm. Dissolution samples should be collected at 5 min, 10 min, 15 min and 20 min.

Sincerely yours,

/S/

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

CC: ANDA 76-241
ANDA DUPLICATE
DIVISION FILE
FIELD COPY
DRUG FILE

HFD-652/ J. Chaney
HFD-652/ Y. Huang
HFD-617/ K. Scardina
HFD-650/ D. Conner

S 11/27/2001
11/28/2001
12/4/01
11/30/01

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BIOEQUIVALENCY – INCOMPLETE Submission date: September 20, 2001

1. FASTING STUDY (STF) olc Strength: 15 mg
Outcome: AC

Clinical:

Analytical:

2. FOOD STUDY (STP) olc Strength: 15 mg
Outcome: AC

Clinical:

Analytical:

3. DISSOLUTION WAIVER (DIW) olc Strength: 30 mg
Outcome: UN

4. DISSOLUTION WAIVER (DIW) olc Strength: 45 mg
Outcome: UN

NOTE:

AC - Acceptable
NC - No Action
UN - Unacceptable
IC - Incomplete

Outcome Decision: Incomplete

WINBIO COMMENTS:
The biostudies was found acceptable and the dissolution testing was unacceptable.

BIOEQUIVALENCY COMMENTS

ANDA: 76-241 APPLICANT: Amide Pharmaceutical, 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 II (Paddle) at 50 rpm. The test product should meet the following specifications:
>
> Not less than —(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,

/S/

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

#7

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA # 76-241 SPONSOR : Amide Pharmaceutical, Inc.
DRUG AND DOSAGE FORM: Mirtazapine Tablets
STRENGTH(S): 15 mg, 30 mg, 45 mg
TYPES OF STUDIES: Fasting, postprandial and dissolution
CINICAL STUDY SITE: [redacted]

ANALYTICAL SITES: [redacted]

STUDY SUMMARY: Fasting and postprandial studies are acceptable

DISSOLUTION: Acceptable.

DSI INSPECTION STATUS

Inspection needed: No	Inspection status:	Inspection results:
First Generic No New facility No For cause _____ Other _____	Inspection requested: (date) Inspection completed: (date)	

PRIMARY REVIEWER: James Chaney BRANCH: I
INITIAL: JC DATE: 1/30/02

TEAM LEADER: Yih-Chain Huang BRANCH: I
INITIAL: YCH DATE: 1/30/2002

DIRECTOR, DIVISION OF BIOEQUIVALENCE: DALE P. CONNER, Pharm.D.
INITIAL : DPC DATE : 1/31/02

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

76-241

ADMINISTRATIVE DOCUMENTS

76-241

M E M O R A N D U M

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

IC COMPLETED JUN 2 0 2002

DATE: June 12, 2002

FROM: Russell Katz, M.D. /S/ 6/20
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:

[redacted]

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):

[redacted]

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 "depression".

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:

76-241

CORRESPONDENCE

Amide
PHARMACEUTICAL, INC.

101 East Main Street
Little Falls, New Jersey 07424

Telephone (973) 890-1440
Fax (973) 890-7980

July 8, 2003

Mr. Gary Buehler
Director
Office of Generic Drugs
CDER, FDA
Metropark North II
7500 Standish Place, Room 150
Rockville, MD 20855

NDA NO. 76-241 REF NO. SL-001
NDA SUPPL FOR Labeling

LABELING AMENDMENT

RE: ANDA -76-241
Mirtazapine Tablets, 15 mg, 30 mg and 45 mg

Dear Mr. Buehler:

In reference to the our ANDA 76-241 for Mirtazapine Tablets 15 mg, 30 mg ad 45 mg, enclosed please find twelve copies of final printed labeling.

This supplement is in response to our commitment in our ANDA to submit final printed labeling.

Please direct any written communications regarding this ANDA to me at the above address. If you need to call or fax me, my phone number is 973-890-1440 and 973-890-7980 (fax).

Thank you for your attention to this matter.

Sincerely Yours
AMIDE PHARMACEUTICAL, INC.

Jasmine Shah, M.S., R.Ph.
Director Regulatory Affairs

Enc.

RECEIVED
JUL 09 2003
OGD/CDER

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

Amide
PHARMACEUTICAL, INC.

101 East Main Street
Little Falls, New Jersey 07424

Telephone (973) 890-1440
Fax (973) 890-7980

June 11, 2003

Gary Buehler
Director
Office of Generic Drugs
CDER, FDA
Metropark North II
7500 Standish Place, Room 150
Rockville, MD 20855

ORIG AMENDMENT
N/AM

Telephone Amendment

RE: ANDA - 76-241
Mirtazapine Tablets 15 mg, 30 mg and 45 mg

Dear Mr. Buehler:

Per my telephone conversation with Ms. Radhika Rajgopalan, Review Chemist, Office of Generic Drugs, enclosed find the revised analytical method for the API, Mirtazapine. The equation for the calculation of assay and [redacted] per your recommendations. Also, an additional [redacted] method is added to the [redacted] method as per update from the manufacturer.

Please direct any written communications regarding this ANDA to me at the above address. If you need to call or fax me, my phone numbers are 973-890-1440 and 973-890-7980 (fax).

Sincerely,
Amide Pharmaceutcial, Inc.

Jasmine Shah, MS, R.Ph.
Director Regulatory Affairs

Enc.

RECEIVED
JUN 12 2003
OGD / CDER

Amide
PHARMACEUTICAL, INC.

101 East Main Street
Little Falls, New Jersey 07424

Telephone (973) 890-1440
Fax (973) 890-7980

May 28, 2003

ORIG AMENDMENT

N/am

Gary Buehler
Director
Office of Generic Drugs
CDER, FDA
Metropark North II
7500 Standish Place, Room 150
Rockville, MD 20855

MINOR AMENDMENT - FINAL APPROVAL REQUESTED

RE: ANDA - 76-241
Mirtazapine Tablets 15 mg, 30 mg and 45 mg

Dear Mr. Buehler:

Amide Pharmaceutical, Inc. ("AMIDE") submits a Minor Amendment - Final Approval Requested for our pending ANDA Application for Mirtazapine Tablets.

Amide had received a Tentative Approval on Feb 12, 2003 for our Mirtazapine Tablets. Amide is requesting final approval based on the following:

1. Patent number 5,977,099 listed in the Orange Book was deemed as invalid or not infringed in connection with another application by Teva Pharmaceutical (ANDA# 76-119). The ANDA application for Teva was approved on Jan 24, 2003 and the 180-day exclusivity will expire on June 16, 2003. Enclosed as Attachment I is the Orange Book Listing for Teva and a copy of their court decision finding the non infringement of the 099 patent.

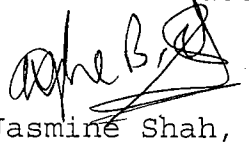
2. Organon, the holder of the patent has requested dismissal of its case against Amide concerning Mirtazapine. Enclosed as Attachment II is a copy of the motion by Organon to dismiss the case.

3. No changes to the labeling have been made since the tentative approval of the ANDA.

RECEIVED
MAY 29 2003
OGD / CDER

Please direct any written communications regarding this ANDA to me at the above address. If you need to call or fax me, my phone numbers are 973-890-1440 and 973-890-7980 (fax).

Sincerely,
Amide Pharmaceutcial, Inc.



Jasmine Shah, MS, R.Ph.
Director Regulatory Affairs

Enc.

Amide
PHARMACEUTICAL, INC.

101 East Main Street
Little Falls, New Jersey 07424

Telephone (973) 890-1440
Fax (973) 890-7980

January 14, 2003

Gary Buehler
Director
Office of Generic Drugs
CDER, FDA
Metropark North II
7500 Standish Place, Room 150
Rockville, MD 20855

Telephone Amendment

ORIG AMENDMENT
N/AC

RE: ANDA - 76-241
Mirtazapine Tablets 15 mg, 30 mg and 45 mg

Dear Mr. Buehler:

Per my telephone conversation with Ms. Nicole Park, Project Manager, Office of Generic Drugs, Amide has completed testing of room temperature stability samples for dissolution test using the following conditions:

> 900 ml of 0.1 N HCl, at 37 C using USP Apparatus II (Paddle) at 50 rpm. Limit: Not less than — (Q) of the labeled amount of Mirtazapine in the dosage form is dissolved in 15 minutes.

Enclosed in Attachment I is a summary of the dissolution test results for test using the revised method. Enclosed in Attachment II is a copy of the updated stability report for Mirtazapine Tablets 15 mg, 30 mg and 45 mg.

Also, enclosed in Attachment III is a copy of the revised analytical method for Mirtazapine Tablets 15 mg, 30 mg and 45 mg.

Please direct any written communications regarding this ANDA to me at the above address. If you need to call or fax me, my phone numbers are 973-890-1440 and 973-890-7980 (fax).

Sincerely,
Amide Pharmaceutcial, Inc.

Jasmine Shah, MS, R.Ph.
Director Regulatory Affairs

Enc.

RECEIVED
JAN 15 2003
OGD / CDER

001

Amide
PHARMACEUTICAL, INC.

101 East Main Street
Little Falls, New Jersey 07424

Telephone (973) 890-1440
Fax (973) 890-7980

NEW CORRESP

NC/Bio

December 30, 2002

Gary Buehler
Director
Office of Generic Drugs
CDER, FDA
Metropark North II
7500 Standish Place, Room 150
Rockville, MD 20855

Telephone Amendment

RE: ANDA - 76-241
Mirtazapine Tablets 15 mg, 30 mg and 45 mg

Dear Mr. Buehler:

Per your letter of December 30, 2002, Amide acknowledges that the following dissolution testing will be incorporated in our stability and quality control program:

The dissolution studies will be conducted in 900 ml of 0.1 N HCl, at 37 C using USP Apparatus II (Paddle) at 50 rpm. The test product will meet the following specifications:

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

Amide affirms to comply with these specifications for all future testing.

Please direct any written communications regarding this ANDA to me at the above address. If you need to call or fax me, my phone numbers are 973-890-1440 and 973-890-7980 (fax).

Sincerely,
Amide Pharmaceutcial, Inc.

Jasmine Shah, MS, R.Ph.
Director Regulatory Affairs

Enc.

RECEIVED
DEC 3 1 2002
OGD / CDER

Amide
PHARMACEUTICAL, INC.

101 East Main Street
Little Falls, New Jersey 07424

Telephone (973) 890-1440
Fax (973) 890-7980

December 19, 2002

Gary Buehler
Director
Office of Generic Drugs
CDER, FDA
Metropark North II
7500 Standish Place, Room 150
Rockville, MD 20855

NEW CORRESP
NC

AMENDMENT

RE: ANDA - 76-241
Mirtazapine Tablets 15 mg, 30 mg and 45 mg

Dear Mr. Buehler:

As per my telephone conversation with Ms. Nicole Park, Project Manager, Office of Generic Drugs for our pending ANDA Application for Mirtazapine Tablets, enclosed find the following:

1. *Revised Exclusivity Certification*
2. *Copy of the Cover page for the Summons served by Organon*

Please direct any written communications regarding this ANDA to me at the above address. If you need to call or fax me, my phone numbers are 973-890-1440 and 973-890-7980 (fax).

Sincerely,
Amide Pharmaceutcial, Inc.

Jasmine Shah, MS, R.Ph.
Director Regulatory Affairs

Enc.

RECEIVED
DEC 2 0 2002
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E Thomas
12/13/2

Amide
PHARMACEUTICAL, INC.

101 East Main Street
Little Falls, New Jersey 07424

Telephone (973) 890-1440
Fax (973) 890-7980

December 11, 2002

Gary Buehler
Director
Office of Generic Drugs
CDER, FDA
Metropark North II
7500 Standish Place, Room 150
Rockville, MD 20855

NEW CORRESP

NC

PATENT AMENDMENT

RE: ANDA - 76-241
Mirtazapine Tablets 15 mg, 30 mg and 45 mg

Dear Mr. Buehler:

Amide Pharmaceutical, Inc. ("AMIDE") submits a Patent Amendment for our pending ANDA Application for Mirtazapine Tablets.

In reference to the notice sent to Organon regarding Paragraph IV Certification, Amide was served with a Complaint for Patent Infringement (for patent no. 5977099) on January 22,2002. The Civil Action No. is 02CV0190(FSH). The notice was filed in the United States District Court For the District of New Jersey and currently the case is being litigated. Amide will notify the FDA as soon as a court decision or a settlement is made.

Please direct any written communications regarding this ANDA to me at the above address. If you need to call or fax me, my phone numbers are 973-890-1440 and 973-890-7980 (fax).

Sincerely,
Amide Pharmaceutcial, Inc.

Jasmine Shah, MS, R.Ph.
Director Regulatory Affairs

Enc.

RECEIVED
DEC 12 2002
OGD / CDER

Amide
PHARMACEUTICAL, INC.

101 East Main Street
Little Falls, New Jersey 07424

Telephone (973) 890-1440
Fax (973) 890-7980

November 8, 2002

Gary Buehler
Director
Office of Generic Drugs
CDER, FDA
Metropark North II
7500 Standish Place, Room 150
Rockville, MD 20855

ORIG AMENDMENT
N/AF

FPL

LABELING AMENDMENT

RE: ANDA -76-241
Mirtazapine Tablets, 15 mg, 30 mg and 45 mg

Dear Mr. Buehler:

In reference to the labeling deficiency letter dated September 30, 2002 from Ms. Michelle Dillahunt, enclosed please find the responses as follows:

Labeling Deficiencies:

1. Blister: Ensure that the established name and strength appear as the most prominent information.

Response: The established name and strength was bolded to appear as the most prominent information.

Enclosed, please find the revised unit dose blister labels with the recommended revisions. **(Attachment 1)**

2. INSERT

Due to changes in the insert labeling of the reference-listed drug, (Remeron® (NDA 20-415)-Organon, Inc, approved September 30, 2002), please revise your labeling as follows:

The insert labeling is revised as recommended. Enclosed, please find the insert comparisons between the previously submitted and revised insert with differences annotated **(Attachment 2)** with the following changes:

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PRECAUTIONS

a. Increased Appetite/Weight Gain

Please add the following sentence as the last sentence;

In an 8-week long pediatric clinical trial of doses between 15-45 mg/day, 49% of mirtazapine-treated patients had a weight gain of at least 7%, compared to 5.7% of placebo treated patients (see PRECAUTIONS-Pediatric Use).

Response: Revised the insert, (PRECAUTIONS-Increased Appetite/Weight Gain) to add above-mentioned sentence as the last sentence.

b. Pediatric Use

Please add the following sentence as the last sentence;

In an 8-week long pediatric clinical trial of doses between 15-45 mg/day, 49 % of mirtazapine-treated patients had a weight gain of at least 7%, compared to 5.7% of placebo treated patients.

Response: Revised the insert, (PRECAUTIONS-Pediatric Use) to add above-mentioned sentence as the last sentence.

Enclosed please find twelve (12) copies each of final mock-up proofs of the insert and blister.

Please direct any written communications regarding this ANDA to me at the above address. If you need to call or fax me, my phone number is 973-890-1440 and 973-890-7980 (fax).

Thank you for your attention to this matter.

Sincerely Yours
AMIDE PHARMACEUTICAL, INC.

Jasmine Shah, M.S., R.Ph.
Director Regulatory Affairs

Enc.

Amide
PHARMACEUTICAL, INC.

101 East Main Street
Little Falls, New Jersey 07424

Telephone (973) 890-1440
Fax (973) 890-7980

January 7, 2002

Gary Buehler
Director
Office of Generic Drugs
CDER, FDA
Metropark North II
7500 Standish Place, Room 150
Rockville, MD 20855

N/A76

ORIG AMENDMENT

Bioequivalency Amendment

RE: ANDA - 76-241
Mirtazapine Tablets 15 mg, 30 mg and 45 mg

Dear Mr. Buehler:

Per your Bioequivalency Amendment letter, of December 17, 2001, enclosed find comparative dissolution studies in the recommended media, 900 ml of 0.1 N HCl for all Mirtazapine Tablets 15 mg, 30 mg and 45 mg.

Please direct any written communications regarding this ANDA to me at the above address. If you need to call or fax me, my phone numbers are 973-890-1440 and 973-890-7980 (fax).

Sincerely,
Amide Pharmaceutcial, Inc.

Jasmine Shah, MS, R.Ph.
Director Regulatory Affairs

Enc.

CENTER FOR DRUG EVALUATION AND RESEARCH
JAN 09 2002
OGD

Amide
PHARMACEUTICAL, INC.

101 East Main Street
Little Falls, New Jersey 07424

Telephone (973) 890-1440
Fax (973) 890-7980

November 9, 2001

Gary Buehler
Director
Office of Generic Drugs
CDER, FDA
Metropark North II
7500 Standish Place, Room 150
Rockville, MD 20855

NEW CORRESP
nc

RE: ANDA - 76-241 ADDITIONAL INFORMATION
Mirtazapine Tablets 15 mg, 30 mg and 45 mg

Dear Mr. Buehler:

Per my telephone conversation with Ms. Beth Fritsch, of November 7, 2001, enclosed find the follows:

1. Revised Exclusivity Statement
2. Breakdown of Opadry Components

Please direct any written communications regarding this ANDA to me at the above address. If you need to call or fax me, my phone numbers are 973-890-1440 and 973-890-7980 (fax).

Sincerely,
Amide Pharmaceutcial, Inc.

Jasmine Shah, MS, R.Ph.
Director Regulatory Affairs

CENTER FOR DRUG
NOV 15 2001
OGD
EVALUATION AND RESEARCH

Enc.

Amide
PHARMACEUTICAL, INC.

101 East Main Street
Little Falls, New Jersey 07424

Telephone (973) 890-1440
Fax (973) 890-7980

October 23, 2001

Gary Buehler
Director
Office of Generic Drugs
CDER, FDA
Metropark North II
7500 Standish Place, Room 150
Rockville, MD 20855

NC

NEW CORRESP

PAPER AND ELECTRONIC

RE: ANDA - 76-241 ORIGINAL APPLICATION
Mirtazapine Tablets 15 mg, 30 mg and 45 mg

Dear Mr. Buehler:

Amide Pharmaceutical, Inc. ("AMIDE") submits today an electronic application ("ANDA") seeking approval to market Mirtazapine Tablets.

The Original application for this product was submitted to FDA on September 20, 2001. Enclosed is electronic version of the application.

Included in the file are:

1. Signed Form 356h
2. Signed certificate stating the data in the electronic portion of the application is same as the paper copy to the best of our knowledge.
3. Following Compact diskettes: Two (2) diskettes each consist of all information required by EVA and Two (2) diskettes each containing Companion document for CMC and BA/BE respectively.
4. Corrected pages 055, 2932, 2935, 3013, 3016, 3018, 3329 and 3331 of the original application. (These are revised due to typo errors).

Please direct any written communications regarding this ANDA to me at the above address. If you need to call or fax me, my phone numbers are 973-890-1440 and 973-890-7980 (fax).

CENTER FOR DRUG EVALUATION AND RESEARCH
OCT 25 2001
OGD

Sincerely,
Amide Pharmaceutcial, Inc.

Jasmine Shah, MS, R.Ph.
Director Regulatory Affairs

Enc.

Amide
PHARMACEUTICAL, INC.

101 East Main Street
Little Falls, New Jersey 07424

Telephone (973) 890-1440
Fax (973) 890-7980

NAE MAR 1-23-02

January 14, 2002

NEW CORRESP
NC

Gary Buehler
Director
Office of Generic Drugs
CDER, FDA
Metropark North II
7500 Standish Place, Room 150
Rockville, MD 20855

PATENT AMENDMENT

RE: ANDA - 76-241
Mirtazapine Tablets 15 mg, 30 mg and 45 mg

Dear Mr. Buehler:

Amide Pharmaceutical, Inc. ("AMIDE") submits a Patent Amendment for our pending ANDA Application for Mirtazapine Tablets.

Included in the file are:

1. Signed Form 356h
2. Amendment to ANDA 76-241(Notice Provided)
3. Amendment to ANDA 76-241 (Evidence of Notification)
4. Amended Patent Certification

Please direct any written communications regarding this ANDA to me at the above address. If you need to call or fax me, my phone numbers are 973-890-1440 and 973-890-7980 (fax).

Sincerely,
Amide Pharmaceutcial, Inc.

Jasmine Shah, MS, R.Ph.
Director Regulatory Affairs

Enc.

CENTER FOR DRUG EVALUATION AND RESEARCH
JAN 16 2002

Amide
PHARMACEUTICAL, INC.

101 East Main Street
Little Falls, New Jersey 07424

Telephone (973) 890-1440
Fax (973) 890-7980

October 21, 2002

Gary Buehler
Director
Office of Generic Drugs
CDER, FDA
Metropark North II
7500 Standish Place, Room 150
Rockville, MD 20855

LABELING AMENDMENT
ORIG AMENDMENT
N/A

RE: ANDA -76-241
Mirtazapine Tablets, 15 mg, 30 mg and 45 mg

Dear Mr. Buehler:

In reference to the labeling deficiency letter dated September 30, 2002 from Ms. Michelle Dillahunt, enclosed please find the responses as follows:

Labeling Deficiencies:

1. UNIT DOSE BLISTER

   a. We encourage the inclusion of a NDC number on your unit dose blister labels.

Response: The NDC number is included as recommended on the unit dose blister labels.

   b. Please increase the font size of your established name and strength.

Response: The font size of the established name and strength was increased on the unit dose blister labels as recommended.

Enclosed, please find the revised unit dose blister labels with the recommended revisions. **(Attachment 1)**

2. INSERT
   a. GENERAL COMMENTS
      Upon further review, we ask that you make the additional following revisions:

The insert labeling is revised as recommended. Enclosed, please find the insert comparisons between the previously submitted and revised insert with differences annotated **(Attachment 2)** with the following changes:

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b. DESCRIPTION

i. Revise the first sentence to read: "Mirtazapine Tablets are an orally administered drug".

Response: Revised the first sentence to read: "Mirtazapine Tablets are an orally administered drug".

ii. Revise the second and third sentence to read: "Mirtazapine has a tetracyclic chemical structure and belongs to the piperazino-azepine group of compounds."

Response: Revised the second and third sentence to read: "Mirtazapine has a tetracyclic chemical structure and belongs to the piperazino-azepine group of compounds."

c. CLINICAL PHARMACOLOGY

i. Pharmacodynamics first sentence; replace [redacted] with "drugs effective in the treatment of major depressive disorder,".

Response: Revised Pharmacodynamics first sentence; and replaced [redacted] with "drugs effective in the treatment of major depressive disorder,".

ii. Clinical Trials Showing Effectiveness-third sentence, replace [redacted] with "Depression" (Hamilton Depression Rating Scale and Montgomery and Asberg Depression Rating Scale)

Response: Revised Clinical Trials Showing Effectiveness-third sentence, and replaced [redacted]" with "Depression" (Hamilton Depression Rating Scale and Montgomery and Asberg Depression Rating Scale)

d. INDICATIONS AND USAGE

i. Third paragraph, first sentence; delete [redacted]

Response: Revised the third paragraph, first sentence; and deleted [redacted]

ii. Third paragraph-second sentence; replace " [redacted] with "re-evaluate".

Response: Revised the third paragraph-second sentence; and replaced ' [redacted] with "re-evaluate".

e. WARNINGS

MAO Inhibitors-revise the first sentence to read;
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.....

Response: Revised WARNINGS, MAO Inhibitors-revised the first sentence to read as above.

f. PRECAUTIONS

i. Suicide-second sentence; replace ' [redacted] with "drugs effective in the treatment of major depressive disorder,....."

Response: Revised the insert PRECAUTIONS Suicide-second sentence; and replaced " [redacted] with "drugs effective in the treatment of major depressive disorder,....."

ii. Use in Patients with Concomittant Illness-second paragraph; delete the second sentence, [redacted]

Response: Revised the Use in Patients with Concomittant Illness-second paragraph; and deleted the second sentence, [redacted]

g. ADVERSE REACTIONS

Nervous System-replace " [redacted] with "depression".

Response: Revised ADVERSE REACTIONS Nervous System-and replaced [redacted] with "depression".

h. OVERDOSAGE
Overdosage Management, first paragraph; replace " [redacted] with "drug effective in the treatment of major depressive disorder".

Response: Revised OVERDOSAGE; sub-paragraph Overdosage Management; first paragraph; and replaced [redacted] with "drug effective in the treatment of major depressive disorder".

i. DOSAGE AND ADMINISTRATION

Initial Treatment
Revise the second and third sentence of the first paragraph to read, "In the controlled clinical trials, establishing the efficacy of mirtazapine in the treatment of major depressive disorder, the effective dose range was generally 15-45 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".

Response: Revised DOSAGE AND ADMINISTRATION Initial Treatment: the second and third sentence of the first paragraph to read as above.

Enclosed please find twelve (12) copies of final mock-up proofs of the insert.

Please direct any written communications regarding this ANDA to me at the above address. If you need to call or fax me, my phone number is 973-890-1440 and 973-890-7980 (fax).

Thank you for your attention to this matter.

Sincerely Yours
AMIDE PHARMACEUTICAL, INC.

Jasmine Shah, M.S., R.Ph.
Director Regulatory Affairs

Enc.

Amide PHARMACEUTICAL, INC.

101 East Main Street
Little Falls, New Jersey 07424

Telephone (973) 890-1440
Fax (973) 890-7980

August 26, 2002

Mr. Gary Buehler
Director
Office of Generic Drugs
CDER, FDA
Metropark North II
7500 Standish Place, Room 150
Rockville, MD 20855

ORIG AMENDMENT

N/A

LABELING AMENDMENT

RE: ANDA -76-241
Mirtazapine Tablets, 15 mg, 30 mg and 45 mg

Dear Mr. Buehler:

In reference to the labeling deficiency letter dated July 5, 2002 from Mr. Adolph Vezza, enclosed please find the responses as follows:

Labeling Deficiencies:

UNIT DOSE BLISTER
We note that you have not submitted unit dose blister labels with the revision "Tablet" (rather than "[redacted]" as previously directed. Please submit.

Response: Enclosed **(Attachment 1)**, please find the revised unit dose blister labels with the revision "Tablet" (rather than "[redacted]"

INSERT
a. GENERAL COMMENTS

i. Due to changes in the labeling of the reference listed drug, Remeron®, approved April 9, 2002, please make the revisions as seen below.

Response: Enclosed **(Attachment 2)**, please find the insert comparisons between the previously submitted and revised insert with differences annotated with the following changes:

ii. Replace the word ' [redacted] with the words "major depressive disorder" throughout the insert except where indicated below.

Response: Replaced the word " [redacted] with the words "major depressive disorder" throughout the insert except where indicated below.

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b. INDICATIONS AND USAGE

i. Third paragraph - The sentence beginning "The antidepressant ..." begins a new paragraph.

Response: Revised the third paragraph: The sentence beginning "The antidepressant ..." begins as a new paragraph.

ii. Delete the sentence "

Response: Revised the insert and deleted the sentence

iii. Let the last sentence to be a part of the paragraph beginning "The antidepressant ..." and revise it to read "... adequately studied. The physician who... individual patient."

Response: Revised the insert, the last sentence to be a part of the paragraph beginning "The antidepressant ..." and revised it to read "... adequately studied. The physician who... individual patient."

c. ADVERSE REACTIONS

i. ECG Changes - Delete the text of this subsection and replace with the following text:

> 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.

Response: Revised the text of this subsection and replaced with the above text.

ii. Add the following text as the last subsection of this section:

> **Other Adverse Events Observed During Postmarketing Evaluation of Mirtazapine.**
> Adverse events reported since market introduction, which were temporarily (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.

Response: Revised the subsection and added the above text as the last subsection of this section.

d. DOSAGE AND ADMINISTRATION
Maintenance/Extended Treatment-Delete the text of this subsection and replace with the following text:

> 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.

Response: Revised the insert and replaced the above text as the revised subsection.

Enclosed please find revised twelve (12) copies of final printed inserts.

Please direct any written communications regarding this ANDA to me at the above address. If you need to call or fax me, my phone number is 973-890-1440 and 973-890-7980 (fax).

Thank you for your attention to this matter.

Sincerely Yours
AMIDE PHARMACEUTICAL, INC.

Jasmine Shah, M.S., R.Ph.
Director Regulatory Affairs

Enc.

Amide
PHARMACEUTICAL, INC.

101 East Main Street
Little Falls, New Jersey 07424

Telephone (973) 890-1440
Fax (973) 890-7980

August 20, 2002

N/A~~A~~C

ORIG AMENDMENT

Gary Buehler
Director
Office of Generic Drugs
CDER, FDA
Metropark North II
7500 Standish Place, Room 150
Rockville, MD 20855

ADDITIONAL INFORMATION AS PER
MR. RON BROWN

RE: ANDA - 76-241
Mirtazapine Tablets 15 mg, 30 mg and 45 mg

Dear Mr. Buehler:

Per my telephone conversation, with Mr. Ron Brown on August 19, 2002, enclosed find two copies for the following:

1. A copy of the revised specification and method for the drug substance (Attachment I).

2. A copy of the revised specification and method for finish product and stability test (Attachment 2).

Please direct any written communications regarding this ANDA to me at the above address. If you need to call or fax me, my phone numbers are 973-890-1440 and 973-890-7980 (fax).

Sincerely,
Amide Pharmaceutcial, Inc.

Jasmine Shah, MS, R.Ph.
Director Regulatory Affairs

Enc.

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Amide
PHARMACEUTICAL, INC.

101 East Main Street
Little Falls, New Jersey 07424

Telephone (973) 890-1440
Fax (973) 890-7980

labeling review drafted 7/4/02 A. Vega

June 6, 2002

Gary Buehler
Director
Office of Generic Drugs
CDER, FDA
Metropark North II
7500 Standish Place, Room 150
Rockville, MD 20855

ORIG AMENDMENT

Minor Deficiency

RE: ANDA - 76-241
Mirtazapine Tablets 15 mg, 30 mg and 45 mg

Dear Mr. Buehler:

Per your Minor Amendment letter, of February 21, 2002, enclosed find our response as follows:

1. [redacted]

batch to batch. Please submit testing protocol.

Response: [redacted] revised. Enclosed find copies of the revised testing protocol for the [redacted] (Attachment 1).

2. [redacted]

Response: Enclosed in Attachment 2 is a copy of the [redacted] component and [redacted] the percent per weight.

JUN 11 2002

OGD / CDER

3. We request that drug substance assay results be reported on the as is [redacted]

Response: The drug substance assay results are tested as [redacted]. The results will be reported as [redacted] Attached in Attachment 3 is a copy of the revised specification and method for the drug substance.

4. We requested that known impurities be identified separately by name rather than "any impurity". In addition, submit chemical names for all related compounds and identify degradation products by chemical names too. Please revise and resubmit drug substance, finish product and stability specifications.

Response: The known impurities are identified separately by name rather than "any impurity". Also, the chemical names for all related compounds and identify degradation products are identified by chemical names. Enclosed is a copy of the revised specification and method for the drug substance (Attachment 3) and the finish product and stability test method (Attachment 4).

Also, the dissolution media has been revised as per the recommendation from the division of bioequivalence. The media has been changed from 0.01 N HCl to 0.1 N HCl.

5. We request you that revise your stability data reporting sheet to identify the finished product test date, not the pull date.

Response: The stability report is revised to include the test date for the finish product testing. Enclosed in Attachment 5 is a copy of the updated room temperature stability data.

Amide notes and acknowledges the following:

1. Since Mirtazapine drug substance and Mirtazapine Tablets are not USP 24 compendial item, method validation will be conducted by a FDA Field laboratory.

2. In the event FDA approves our ANDA prior to the testing of the drug substance and finish product by the FDA laboratory, Amide commits for respond to any deficiency.

LABELING DEFICIENCY

Response to labeling deficiency has been included in Attachment 6. Included in Attachment 6 is annotated comparison of the proposed and final printed labeling. Also, enclosed are twelve copies of the final printed labels and package inserts.

Please direct any written communications regarding this ANDA to me at the above address. If you need to call or fax me, my phone numbers are 973-890-1440 and 973-890-7980 (fax).

Sincerely,
Amide Pharmaceutcial, Inc.

Jasmine Shah, MS, R.Ph.
Director Regulatory Affairs

Enc.

ANDA 76-241

Amide Pharmaceutical, Inc.
Attention: Jasmine Shah
101 East Main Street
Little Falls, NJ 07424

NOV 14 2001

Dear Sir:

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

Reference is made to the telephone conversation dated November 6, 2001 and your correspondence dated November 8, 2001.

NAME OF DRUG: Mirtazapine Tablets, 15 mg, 30 mg and 45 mg

DATE OF APPLICATION: September 20, 2001

DATE (RECEIVED) ACCEPTABLE FOR FILING: September 20, 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:

Stanley Shepperson
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

505(j)(2)(a)
11/14/01
ack

Amide
PHARMACEUTICAL, INC.

101 East Main Street
Little Falls, New Jersey 07424

Telephone (973) 890-1440
Fax (973) 890-7980

September 20, 2001

Gary Buehler
Director
Office of Generic Drugs
CDER, FDA
Metropark North II
7500 Standish Place, Room 150
Rockville, MD 20855

PAPER AND ELECTRONIC

RE: ANDA - ORIGINAL APPLICATION
Mirtazapine Tablets 15 mg, 30 mg and 45 mg

Dear Mr. Buehler:

Enclosed please find Amide Pharmaceutical's original Drug Application for Mirtazapine Tablets 15 mg, 30 mg and 45 mg and a transmittal letter (and one copy) describing same.

Kindly, have the copy of the transmittal letter stamped "filed" and return it to our courier who has been instructed to wait.

Thank you for your attention to this matter.

Very truly yours,

Jasmine Shah, MS, R.Ph.
Director, Regulatory Affairs

CENTER FOR DRUGS
SEP 20 2001
EVALUATION AND RESEARCH

Amide
PHARMACEUTICAL, INC.

101 East Main Street
Little Falls, New Jersey 07424

Telephone (973) 890-1440
Fax (973) 890-7980

September 20, 2001

Gary Buehler
Director
Office of Generic Drugs
CDER, FDA
Metropark North II
7500 Standish Place, Room 150
Rockville, MD 20855

PAPER AND ELECTRONIC

RE: ANDA - ORIGINAL APPLICATION
Mirtazapine Tablets 15 mg, 30 mg and 45 mg

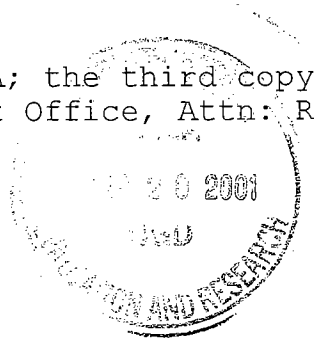
Dear Mr. Buehler:

Pursuant to section 505 (j) of the Food, Drug and Cosmetic Act and amendments thereto, Amide Pharmaceutical, Inc. ("AMIDE") submits today an original abbreviated new drug application ("ANDA") seeking approval to market [redacted] *Mirtazapine Tablets* are generic for the listed drug Remeron Tablet, manufactured for Organon Inc., West Orange, NJ 07052 USA, by N.V.Organon, OSS, The Netherlands pursuant to NDA #20-415.

Included in the file are:

1. All information required by Form 356h including:
   a) Signed Form 356h
   b) Archival Copy (blue folder) - 10 Volumes
   c) Review Copy - CMC (red folder) - 2 Volume
   d) Review Copy - Bioequivalency (Orange folder)- 8 Volumes (4 volumes each for fasting and fed studies)
   e) Three copies of Analytical Method and Validation Report
   f) Four draft copies of product container labels and package inserts

2. A copy of CMC Section of the ANDA; the third copy is being sent to the FDA's Newark District Office, Attn: Regina Brown as required under FDA guidelines.

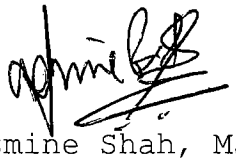


For more detailed information on the organization of the ANDA, please refer to Intro-page iv of the ANDA, "EXECUTIVE SUMMARY- Organization of the ANDA".

An electronic application will also be submitted with the paper application for this product. The electronic application will be submitted within the next 30 days.

Please direct any written communications regarding this ANDA to me at the above address. If you need to call or fax me, my phone numbers are 973-890-1440 and 973-890-7980 (fax).

Sincerely,
Amide Pharmaceutcial, Inc.



Jasmine Shah, MS, R.Ph.
Director Regulatory Affairs

Enc.