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RESEARCH**

APPLICATION NUMBER: 20-415/S-003

FINAL PRINTED LABELING

REMERON™ (mirtazapine) 45 mg

Final Printed Labeling

Package Insert

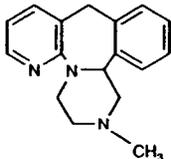
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REMERON™ (mirtazapine) Tablets

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DESCRIPTION

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



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

REMERON™ is supplied for oral administration as film-coated tablets containing 15, 30 or 45 mg of mirtazapine. The 15 mg and 30 mg tablets are scored. Each tablet also contains corn starch, hydroxypropyl cellulose, magnesium stearate, colloidal silicon dioxide, lactose and other inactive ingredients.

CLINICAL PHARMACOLOGY

Pharmacodynamics

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

Evidence gathered in preclinical studies suggests that mirtazapine enhances central noradrenergic and serotonergic activity. These studies have shown that mirtazapine acts as an antagonist at central presynaptic α_2 adrenergic inhibitory autoreceptors and heteroreceptors, an action that is postulated to result in an increase in central noradrenergic and serotonergic activity.

Mirtazapine is a potent antagonist of 5-HT₂ and 5-HT₃ receptors. Mirtazapine has no significant affinity for the 5-HT_{1A} and 5-HT_{1B} receptors.

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

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

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

Pharmacokinetics

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

Mirtazapine is extensively metabolized after oral administration. Major pathways of biotransformation are demethylation and hydroxylation followed by glucuronide conjugation. In vitro data from human liver microsomes indicate that cytochrome 2D6 and 1A2 are involved in the formation of the 8-hydroxy metabolite of mirtazapine, whereas cytochrome 3A is considered to be responsible for the formation of the N-desmethyl and N-oxide metabolite. Mirtazapine has an absolute bioavailability of about

50%. It is eliminated predominantly via urine (75%) with 15% in feces. Several unconjugated metabolites possess pharmacological activity but are present in the plasma at very low levels. The (-) enantiomer has an elimination half-life that is approximately twice as long as the (+) enantiomer and therefore achieves plasma levels that are about three times as high as that of the (+) enantiomer.

Plasma levels are linearly related to dose over a dose range of 15 to 80 mg. The mean elimination half-life of mirtazapine after oral administration ranges from approximately 20–40 hours across age and gender subgroups, with females of all ages exhibiting significantly longer elimination half-lives than males (mean half-life of 37 hours for females vs. 26 hours for males). Steady state plasma levels of mirtazapine are attained within 5 days, with about 50% accumulation (accumulation ratio = 1.5). Mirtazapine is approximately 85% bound to plasma proteins over a concentration range of 0.01 to 10 μ g/mL.

Population Subgroups

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

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

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

Clinical Trials Showing Effectiveness

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

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

INDICATIONS AND USAGE

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

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

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

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

The effectiveness of REMERON™ in long term more than 6 weeks, has not been systematically controlled trials. Therefore, the physician prescribing REMERON™ for extended periods should evaluate the long-term usefulness of the drug for the individual patient.

CONTRAINDICATIONS

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

WARNINGS

Agranulocytosis

In premarketing clinical trials, two (2) cases of Syndrome) out of 2,796 patients treated with REMERON™ (mirtazapine) Tablets developed agranulocytosis (ANC < 500/mm³ with symptoms, e.g., fever, infection, etc) and symptoms, e.g., fever, infection, etc developed severe neutropenia [ANC < 5 associated symptoms]. For these three severe neutropenia was detected on day 4 of treatment, respectively. All three patients were stopped. These three cases of severe neutropenia (with associated infection) of approximately 1.1 per 1000 patients exposed, with a very wide 95% confidence interval of 2.2 cases per 10,000 to 3.1 cases per 100,000 patients exposed, along with a low WBC count, REMERON™ should be discontinued and patients should be closely monitored.

MAO Inhibitors

In patients receiving other antidepressants with a monoamine oxidase inhibitor (MAOI) who have recently discontinued an MAOI and then are started on an MAOI, there are reports of serious, and sometimes fatal, reactions including nausea, vomiting, flushing, dizziness, rigidity, diaphoresis, hyperthermia, and status changes ranging from agitation to coma. There are no human data pertinent to the combination of REMERON™ (mirtazapine) and MAOIs. REMERON™ should not be used in combination with MAOIs within 14 days of initiating or discontinuing MAOI.

PRECAUTIONS

General

Somnolence

In U.S. controlled studies, somnolence was observed in patients treated with REMERON™ (mirtazapine) 18% for placebo and 60% for amitriptyline. Somnolence resulted in discontinuation for 10 treated patients, compared to 2.2% for placebo, whether or not tolerance develops to the REMERON™. Because of REMERON™'s effects on impairment of performance, patients should be cautioned about engaging in activities requiring alertness. Patients have been able to assess the drug's effect on their performance (see Information for Patients).

Dizziness

In U.S. controlled studies, dizziness was observed in patients treated with REMERON™ (mirtazapine) 3% for placebo and 14% for amitriptyline. Dizziness or not tolerance develops to the dizziness with the use of REMERON™.

Increased Appetite/Weight Gain

In U.S. controlled studies, appetite increase was observed in 17% of patients treated with REMERON™ (mirtazapine) compared to 2% for placebo and 6% for amitriptyline. In a pooled analysis, weight gain of $\geq 7\%$ of body weight was observed in patients treated with mirtazapine, compared to 2% for placebo and 5.9% for amitriptyline. In a pooled analysis, including many patients in long-term studies, 8% of patients receiving REMERON™ had a weight gain.

Cholesterol/Triglycerides

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

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RECAUTIONS and DOSAGE

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attempt or suicidal ideation.

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

CONTRAINDICATIONS

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

WARNINGS

Agranulocytosis

In premarketing clinical trials, two (one with Sjögren's
Syndrome) out of 2,796 patients treated with REMERON™
(mirtazapine) Tablets developed agranulocytosis [absolute
neutrophil count (ANC) < 500/mm³ with associated signs
and symptoms, e.g., fever, infection, etc.] and a third patient
developed severe neutropenia [ANC < 500/mm³ without any
associated symptoms]. For these three patients, onset of
severe neutropenia was detected on days 61, 9, and 14 of
treatment, respectively. All three patients recovered after
REMERON™ was stopped. These three cases yield a crude
incidence of severe neutropenia (with or without associ-
ated 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 devel-
ops a sore throat, fever, stomatitis or other signs of in-
fection, along with a low WBC count, treatment with
REMERON™ should be discontinued and the patient
should be closely monitored.

MAO Inhibitors

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

PRECAUTIONS

General

Somnolence

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

Dizziness

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

Increased Appetite/Weight Gain

In U.S. controlled studies, appetite increase was reported in
17% of patients treated with REMERON™ (mirtazapine), com-
pared 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 place-
bo and 5.9% for amitriptyline. In a pool of premarketing U.S.
studies, including many patients in long-term, open label treat-
ment, 8% of patients receiving REMERON™ discontinued for
weight gain.

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 REMERON™ (mirtazapine), compared to
7% for placebo and 8% for amitriptyline. In these same studies,
nonfasting triglyceride increases to ≥ 500 mg/dL were observed
in 6% of patients treated with mirtazapine, compared to 3% for
placebo and 3% for amitriptyline.

Transaminase Elevations

Clinically significant ALT (SGPT) elevations (≥ 3 times the upper
limit of the normal range) were observed in 2.0% (8/424) of
patients exposed to REMERON™ (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
REMERON™ treatment. Mirtazapine should be used with
caution in patients with impaired hepatic function (see
Pharmacokinetics section of CLINICAL PHARMACOLOGY, and
DOSAGE AND ADMINISTRATION).

Activation of Mania/Hypomania

Mania/hypomania occurred in approximately 0.2% (3/1,299
patients) of REMERON™ (mirtazapine) treated patients in U.S.
studies. Although the incidence of mania/hypomania was very
low during treatment with mirtazapine, it should be used care-
fully 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
REMERON™ (mirtazapine). However, no controlled studies
have been carried out in patients with a history of seizures.
Therefore, care should be exercised when mirtazapine is used
in these patients.

Suicide

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

Use in Patients with Concomitant Illness

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

Mirtazapine has not been systematically evaluated or used to
any appreciable extent in patients with a recent history of
myocardial infarction or other significant heart disease.
Mirtazapine was not associated with clinically significant ECG
abnormalities in U.S. and non-U.S. placebo controlled trials.
Mirtazapine was associated with significant orthostatic hypo-
tension in early clinical pharmacology trials with normal volun-
teers. Orthostatic hypotension was infrequently observed in
clinical trials with depressed patients. REMERON™ should be
used with caution in patients with known cardiovascular or cere-
brovascular disease that could be exacerbated by hypotension
(history of myocardial infarction, angina, or ischemic stroke) and
conditions that would predispose patients to hypotension
(dehydration, hypovolemia, and treatment with antihypertensive
medication).

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

Information for Patients

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

Agranulocytosis

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

Interference with Cognitive and Motor Performance

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

Completing Course of

While patients may not
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Concomitant Medication

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Laboratory Tests

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Carcinogenesis

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Tablets are contraindicated in patients with sensitivity to mirtazapine.

In two patients (one with Sjögren's syndrome and one treated with REMERON™ and agranulocytosis [absolute neutrophil count < 500/mm³ without any other signs or symptoms, onset of neutropenia on days 61, 9, and 14 of treatment; three patients recovered after treatment; these three cases yield a crude incidence of 1.1 per thousand patients per year with 95% confidence interval, i.e., 0.2 to 2.1 per 1000. If a patient develops agranulocytosis or other signs of infection, treatment with REMERON™ should be discontinued and the patient

should be treated with an MAOI in combination with an antidepressant drug. In patients receiving an antidepressant drug, there have been reports of reactions, e.g., including dizziness, tremor, myoclonus, ataxia, autonomic instability, seizures, and mental status changes to coma. Although the mechanism of such an interaction is not known, it is recommended that the combination with an MAOI, or discontinuing therapy with an

antidepressant was reported in 54% of patients receiving REMERON™ (mirtazapine), compared to 10.4% of patients receiving amitriptyline. In these studies, somnolence was reported in 7.5% of patients receiving REMERON™ (mirtazapine), compared to 0% for placebo. It is unclear whether the somnolent effects of REMERON™ are potentially significant. In these studies, patients should be cautioned about alertness until they know the effect on their own psychomotor performance.

Weight gain was reported in 7% of patients receiving REMERON™ (mirtazapine), compared to 1.5% for placebo. It is unclear whether the weight gain observed in association

with REMERON™ (mirtazapine) is related to the weight gain reported in 7.5% of patients receiving REMERON™ (mirtazapine), compared to 0% for placebo. In these studies, patients should be cautioned about alertness until they know the effect on their own psychomotor performance.

Cholesterol increases to ≥ 200 mg/dL were observed in 15% of patients receiving REMERON™ (mirtazapine), compared to 3% for placebo. In these studies, patients should be cautioned about alertness until they know the effect on their own psychomotor performance.

Transaminase Elevations

Clinically significant ALT (SGPT) elevations (≥ 3 times the upper limit of the normal range) were observed in 2.0% (8/424) of patients exposed to REMERON™ (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 REMERON™ treatment. Mirtazapine should be used with caution in patients with impaired hepatic function (see Pharmacokinetics section of CLINICAL PHARMACOLOGY, and DOSAGE AND ADMINISTRATION).

Activation of Mania/Hypomania

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

Seizure

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

Suicide

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

Use in Patients with Concomitant Illness

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

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

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

Information for Patients

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

Agranulocytosis

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

Interference with Cognitive and Motor Performance

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

Completing Course of Therapy

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

Concomitant Medication

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

Alcohol

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

Pregnancy

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

Nursing

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

Laboratory Tests

There are no routine laboratory tests recommended.

Drug Interactions

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

Drugs Affecting Hepatic Metabolism

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

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

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

Alcohol

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

Diazepam

Concomitant administration of diazepam (15 mg) had a minimal effect on plasma levels of mirtazapine (15 mg) in 12 healthy subjects. However, the impairment of motor skills produced by REMERON™ (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 REMERON™.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

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

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

Mutagenesis

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

Pregnancy

Teratogenic Effects - Pregnancy Category C

Reproduction studies in pregnant rats and rabbits at doses up to 100 mg/kg and 40 mg/kg, respectively (20 and 17 times the maximum recommended human dose (MRHD) on a mg/m² basis, respectively), have revealed no evidence of teratogenic effects. However, in rats, there was an increase in post-implantation losses in dams treated with REMERON™ (mirtazapine). There was an increase in pup deaths during the first 3 days of lactation and a decrease in pup birth weights. The cause of these deaths is not known. These effects occurred at doses that were 20 times the MRHD, but not at 3 times the MRHD, on a mg/m² basis. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers

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

Pediatric Use

Safety and effectiveness in children have not been established.

Geriatric Use

Approximately 190 elderly individuals (≥ 65 years of age) participated in clinical studies with REMERON™ (mirtazapine). No unusual adverse age-related phenomena were identified in this group. Pharmacokinetic studies revealed a decreased clearance in the elderly. Caution is indicated in administering REMERON™ to elderly patients (see CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION).

ADVERSE REACTIONS

Associated with Discontinuation of Treatment

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

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

Commonly Observed Adverse Events in U.S. Controlled Clinical Trials

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

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

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

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

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

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

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

¹Events reported by at least 1% of patients treated with REMERON™ (mirtazapine) are included, except the following events which had an incidence on placebo ≥ REMERON™: headache, infection, pain, chest pain, palpitation, tachycardia, postural hypotension, nausea, dyspepsia, diarrhea, flatulence, insomnia, nervousness, libido decreased, hypertonia, pharyngitis, rhinitis, sweating, amblyopia, tinnitus, taste perversion.

ECG Changes

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

Other Adverse Events Observed During the Premarketing Evaluation of REMERON™

During its premarketing assessment, multiple doses of REMERON™ (mirtazapine) were administered to 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 the sure were recorded by clinical investigators using term of their own choosing. Consequently, it is not possible to give a meaningful estimate of the proportion of individual patients experiencing adverse events without first grouping similar untoward events into a smaller number of standardized categories.

In the tabulations that follow, reported adverse event classified using a standard COSTART-based dictionary terminology. The frequencies presented, therefore, represent a portion of the 2,796 patients exposed to multiple doses of REMERON™ who experienced an event of the type cited at least one occasion while receiving REMERON™. All events are included except those already listed in the p table, those adverse experiences subsumed under CO terms that are either overly general or excessively specific as to be uninformative, and those events for which a drug was very remote.

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

Events are further categorized by body system and in order of decreasing frequency according to the following definitions: frequent adverse events are those occurring on more occasions in at least 1/100 patients; infrequent adverse events are those occurring in 1/100 to 1/1000 patient events are those occurring in fewer than 1/1000 patient those events not already listed in the previous table on this listing. Events of major clinical importance are described in the WARNINGS and PRECAUTIONS section.

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

Cardiovascular System: frequent: hypertension, vasodilation, glossitis, cholecystitis, nausea and vomiting, gun orrhage, stomatitis, colitis, liver function tests abnormal, tongue discoloration, ulcerative stomatitis, salivary enlargement, increased salivation, intestinal obstruction, pancreatitis, aphthous stomatitis, cirrhosis of liver, gastroenteritis, oral moniliasis, tongue edema.

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

Endocrine System: rare: goiter, hypothyroidism.

Hemic and Lymphatic System: rare: lymphadenopathy, penia, petechia, anemia, thrombocytopenia, lymphocytopenia.

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

Musculoskeletal System: frequent: myasthenia, arthralgia, arthritides, tenosynovitis; rare: pathological fracture, porosis fracture, bone pain, myositis, tendon rupture, art bursitis.

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

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

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

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, menorrhagia, leukorrhea, impotence; rare: polyuria, ure

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

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

Endocrine System: rare: goiter, hypothyroidism.

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

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

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

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

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

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

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

Urogenital System: frequent: urinary tract infection; infrequent: kidney calculus, cystitis, dysuria, urinary incontinence, urinary retention, vaginitis, hematuria, breast pain, amenorrhea, dysmenorrhea, leukorrhea, impotence; rare: polyuria, urethritis,

metrorrhagia, menorrhagia, abnormal ejaculation, breast engorgement, breast enlargement, urinary urgency.

DRUG ABUSE AND DEPENDENCE

Controlled Substance Class

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

Physical and Psychological Dependence

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

OVERDOSAGE

Human Experience

There is very limited experience with REMERON™ (mirtazapine) overdose. In premarketing clinical studies, there were eight reports of mirtazapine overdose alone or in combination with other pharmacological agents. The only drug overdose death reported while taking REMERON™ Tablets was in combination with amitriptyline and chlorprothixene in a non-U.S. clinical study. Based on plasma levels, the REMERON™ dose taken was 30-45 mg, while plasma levels of amitriptyline and 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 REMERON™ alone.

Overdose Management

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

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

DOSAGE AND ADMINISTRATION

Initial Treatment

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

Elderly and Patients with Renal or Hepatic Impairment

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

Maintenance/Extended Treatment

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

Switching Patients To or From Inhibitor

At least 14 days should elapse before MAOI and initiation of therapy with I In addition, at least 14 days should REMERON™ before starting an MA

HOW SUPPLIED

- REMERON™ (mirtazapine) Tablets
- 15 mg Tablets - oval, scored, yellow embossed on one side and "TZ3" on the other
- Bottles of 30 NDC#
- Unit Dose, Box of 100 NDC#
- 30 mg Tablets - oval, scored, "Organon" embossed on one side and "TZ3" on the other
- Bottles of 30 NDC#
- Unit Dose, Box of 100 NDC#
- 45 mg Tablets - oval, white, coated on one side and "TZ7" on the other
- Bottles of 30 NDC#
- Bottles of 100 NDC#
- Bottles of 500 NDC#
- Unit Dose, Box of 100 NDC#

*Unit dose packs are provided as a each of which contains 10 tablets.

Store at controlled Room 20°-25°C (68°-77°F)

Dispense in a tight, light resistant container.

Caution: Federal law prohibits refilling without a new prescription.



Manufactured for Org West Orange, NJ 07067 by N.V. Organon, Oss

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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 close-
ly for signs of mirtazapine misuse or abuse (e.g., development
of tolerance, incrementations of dose, drug-seeking behavior).

OVERDOSAGE

Human Experience

There is very limited experience with REMERON™ (mirtaza-
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Overdose Management

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are no specific antidotes for REMERON™ (mirtazapine). If the
patient is unconscious, establish and maintain an airway to
ensure adequate oxygenation and ventilation. Gastric evacua-
tion either by the induction of emesis or lavage or both should
be considered. Activated charcoal should also be considered in
treatment of overdose. Cardiac and vital signs monitoring is rec-
ommended along with general symptomatic and supportive
measures.

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

DOSAGE AND ADMINISTRATION

Initial Treatment

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tive dose range was generally 15–45 mg/day. While the
relationship between dose and antidepressant response for
REMERON™ has not been adequately explored, patients not
responding to the initial 15 mg dose may benefit from dose
increases up to a maximum of 45 mg/day. REMERON™ has an
elimination half-life of approximately 20–40 hours; therefore,
dose changes should not be made at intervals of less than one
to two weeks in order to allow sufficient time for evaluation of
the therapeutic response to a given dose.

Elderly and Patients with Renal or Hepatic Impairment

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in patients with moderate to severe renal or hepatic impairment.
Consequently, the prescriber should be aware that plasma
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that pharmacological treatment for acute episodes of depres-
sion should continue for up to six months or longer. Whether the
dose of antidepressant needed to induce remission is identical
to the dose needed to maintain euthymia is unknown.

Switching Patients To or From a Monoamine Oxidase Inhibitor

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

HOW SUPPLIED

REMERON™ (mirtazapine) Tablets are supplied as:

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

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

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

Bottles of 30 NDC# 0052-0107-30
Unit Dose, Box of 100 NDC# 0052-0107-90*

45 mg Tablets – oval, white, coated, with "Organon" embossed
on one side and "TZ7" on the other side.

Bottles of 30 NDC# 0052-0109-30
Bottles of 100 NDC# 0052-0109-91
Bottles of 500 NDC# 0052-0109-95
Unit Dose, Box of 100 NDC# 0052-0109-90*

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

Store at controlled Room Temperature
20°–25°C (68°–77°F)

Dispense in a tight, light resistant container.

**Caution: Federal law prohibits dispensing without pre-
scription.**



Manufactured for Organon Inc.
West Orange, NJ 07052
by N.V. Organon, Oss, Holland

5310140 9/96

049

Labeling: SCS-003/FA

NDA No: 20-415 Rec'd. 4-4-9

Reviewed by: [Signature]

APR 17 1997

Labeling: SCS-003
NDA No: 20-415 Rec'd. 11-17-95
Reviewed by: [Signature]

REMERON™ (mirtazapine) Tablets

45 mg

APPROVED

Bottle of 30 Label

MAR 17 1997

Lot/Exp:

Store at controlled room temperature
20°-25°C (68°-77°F).
Dispense in a light-resistant
container as described in the USP.

30 Tablets

NDC 0052-0100-30

45 mg

REMERON™
(mirtazapine)
Tablets



Manufactured for Organon Inc.
West Orange, NJ 07062 USA
by N.V. Organon, Oss, Holland

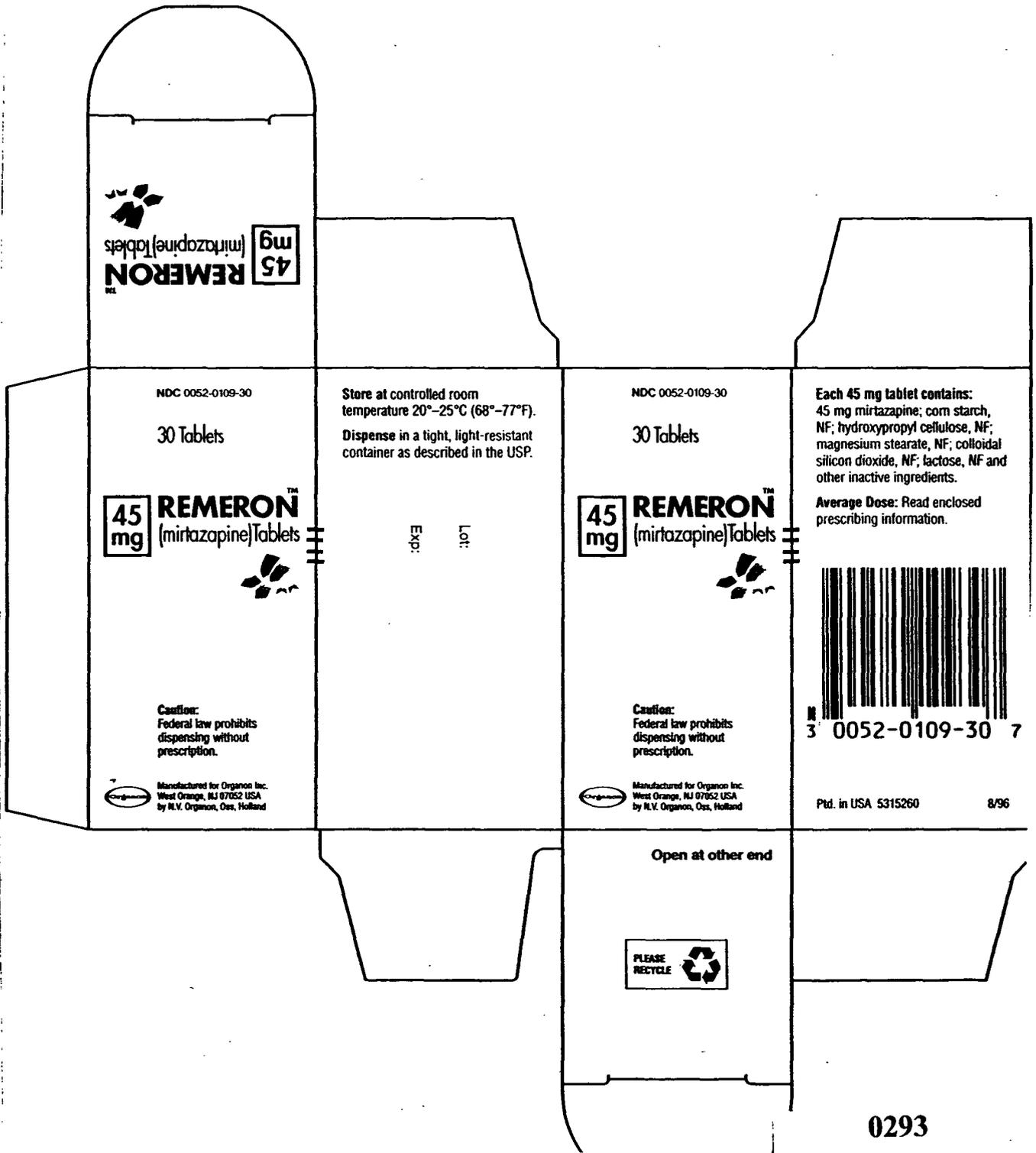
Each 45 mg tablet contains:
45 mg mirtazapine, con. salt, NF;
hydroxypropyl cellulose, NF;
hydroxypropyl methylcellulose, NF;
silicon dioxide, NF; lactose, NF and
other inactive ingredients.
Average Dose: 15 mg increased
gradually to 45 mg.
Caution: Do not take with
other antidepressants
without prescription.
Ph. in USA 530620

45 mg

REMERON™ (mirtazapine) Tablets

45 mg

Bottle of 30 Carton



0293

REMERON™ (mirtazapine) Tablets

45 mg

Bottle of 100 Label

Lot:

Exp:

Store at controlled room temperature 20°–25°C (68°–77°F).

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

100 Tablets

NDC 0052-0109-91

45 mg

REMERON™
(mirtazapine)
Tablets



Manufactured for Organon Inc.
West Orange, NJ 07062 USA
by N.V. Organon, Oss, Holland

Each 45 mg tablet contains:

45 mg mirtazapine; corn starch, NF; hydroxypropyl cellulose, NF; magnesium stearate, NF; colloidal silicon dioxide, NF; lactose, NF and other inactive ingredients.

Average Dose: Read enclosed prescribing information.

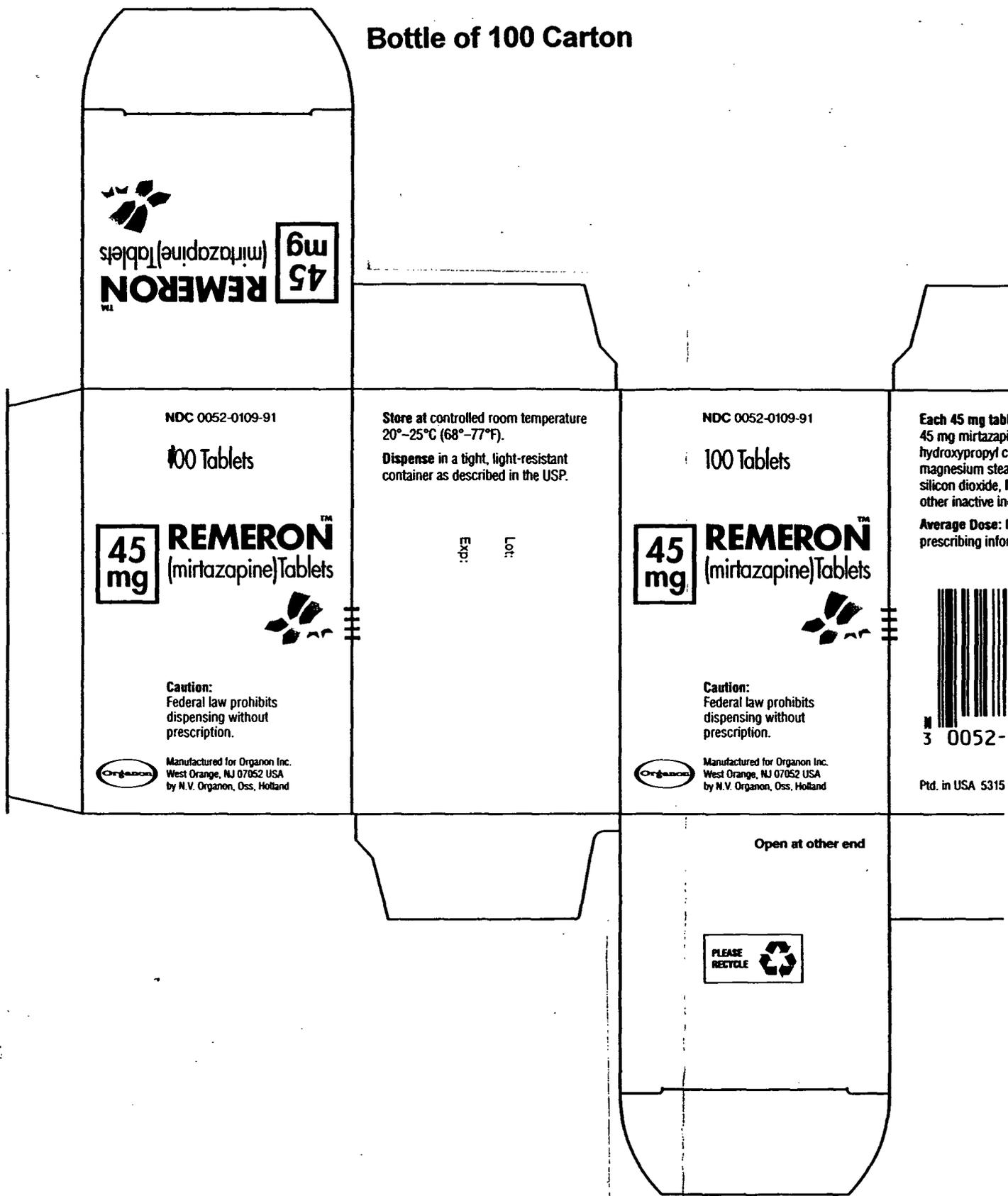
Caution: Federal law prohibits dispensing without prescription.

Pfd. in USA 5308627 8/96

REMERON™ (mirtazapine) Tablets

45 mg

Bottle of 100 Carton




REMERON™
45 mg (mirtazapine) Tablets

NDC 0052-0109-91

100 Tablets

45 mg **REMERON™**
(mirtazapine) Tablets



Caution:
Federal law prohibits
dispensing without
prescription.



Manufactured for Organon Inc.
West Orange, NJ 07052 USA
by N.V. Organon, Oss, Holland

Store at controlled room temperature
20°–25°C (68°–77°F).

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

Exp: Lot:

NDC 0052-0109-91

100 Tablets

45 mg **REMERON™**
(mirtazapine) Tablets



Caution:
Federal law prohibits
dispensing without
prescription.



Manufactured for Organon Inc.
West Orange, NJ 07052 USA
by N.V. Organon, Oss, Holland

Each 45 mg tabl
45 mg mirtazapi
hydroxypropyl c
magnesium stea
silicon dioxide, I
other inactive in
Average Dose: I
prescribing info



3 0052-

Ptd. in USA 5315

Open at other end



REMERON™ (mirtazapine) Tablets

45 mg

Bottle of 100 Carton



NDC 0052-0109-91

100 Tablets

45 mg
REMERON™
(mirtazapine) Tablets



Caution:
Federal law prohibits
dispensing without
prescription.



Manufactured for Organon Inc.
West Orange, NJ 07052 USA
by N.V. Organon, Oss, Holland

Store at controlled room temperature
20°–25°C (68°–77°F).
Dispense in a tight, light-resistant
container as described in the

NDC 0052-0109-91

100 Tablets

REMERON™
(mirtazapine) Tablets



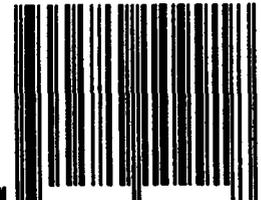
Caution:
Federal law prohibits
dispensing without
prescription.

Manufactured for Organon Inc.
West Orange, NJ 07052 USA
by N.V. Organon, Oss, Holland

Exp:
Lot:

Each 45 mg tablet contains:
45 mg mirtazapine; corn starch, NF;
hydroxypropyl cellulose, NF;
magnesium stearate, NF; colloidal
silicon dioxide, NF; lactose, NF and
other inactive ingredients.

Average Dose: Read enclosed
prescribing information.



3 0052-0109-91 8

Ptd. in USA 5315261

8/96

Open at other end

PLEASE
RECYCLE



0295

REMERON™ (mirtazapine) Tablets

45 mg

Bottle of 500 Label

500
Tablets

NDC 0052-0109-95

**45
mg**

REMERON™
(mirtazapine)
Tablets 

Lot:

Exp:

Store at controlled room temperature 20°-25°C (68°-77°F).
Dispense in a tight, light-resistant container as described
in the USP.



Manufactured for Organon Inc.
West Orange, NJ 07052 USA
by N.V. Organon, Oss, Holland

Each 45 mg tablet contains:
45 mg mirtazapine; corn starch, NF; hydroxypropyl cellulose, NF;
magnesium stearate, NF; colloidal silicon dioxide, NF; lactose, NF
and other inactive ingredients.

Average Dose: Read enclosed prescribing information.

Caution: Federal law prohibits dispensing without prescription.
Ptd. in USA 5308628 8/96

REMERON™ (mirtazapine) Tablets

45 mg

Bottle of 500 Carton



REMERON™
(mirtazapine) Tablets
45 mg

NDC 0052-0109-95

500 Tablets

45 mg **REMERON™**
(mirtazapine) Tablets



Store at controlled room temperature 20°–25°C (68°–77°F).

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

45 mg

Exp:
Lot:

Caution:
Federal law prohibits dispensing without prescription.



Manufactured for Organon Inc.
West Orange, NJ 07052 USA

0297

Store at controlled room temperature 20°-25°C (68°-77°F).

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

Exp:

Lot:

NDC 0052-0109-95

500 Tablets

45 mg **REMERON**TM
(mirtazapine) Tablets



Caution:
Federal law prohibits
dispensing without
prescription.



Manufactured for Organon Inc.
West Orange, NJ 07052 USA
by N.V. Organon, Oss, Holland

Each 45 mg tablet contains:
45 mg mirtazapine; corn starch, NF;
hydroxypropyl cellulose, NF;
magnesium stearate, NF; colloidal
silicon dioxide, NF; lactose, NF
and other inactive ingredients.

Average Dose: Read enclosed
prescribing information.



Ptd. in USA 5315262

5/96

Open at other end

PLEASE
RECYCLE



REMERON™ (mirtazapine) Tablets

45 mg

Unit Dose Blister Label

Exp. Lot	NDC 0052-0100-90 5328249 8/96 Remeron™ (mirtazapine) Tablets Manufactured for Organon Inc. West Orange, NJ 07052 USA by N.V. Organon, Oss, Holland 45 mg	NDC 0052-0100-90 5328249 8/96 Remeron™ (mirtazapine) Tablets Manufactured for Organon Inc. West Orange, NJ 07052 USA by N.V. Organon, Oss, Holland 45 mg	Lot Exp.
Exp. Lot	NDC 0052-0100-90 5328249 8/96 Remeron™ (mirtazapine) Tablets Manufactured for Organon Inc. West Orange, NJ 07052 USA by N.V. Organon, Oss, Holland 45 mg	NDC 0052-0100-90 5328249 8/96 Remeron™ (mirtazapine) Tablets Manufactured for Organon Inc. West Orange, NJ 07052 USA by N.V. Organon, Oss, Holland 45 mg	Lot Exp.
Exp. Lot	NDC 0052-0100-90 5328249 8/96 Remeron™ (mirtazapine) Tablets Manufactured for Organon Inc. West Orange, NJ 07052 USA by N.V. Organon, Oss, Holland 45 mg	NDC 0052-0100-90 5328249 8/96 Remeron™ (mirtazapine) Tablets Manufactured for Organon Inc. West Orange, NJ 07052 USA by N.V. Organon, Oss, Holland 45 mg	Lot Exp.
Exp. Lot	NDC 0052-0100-90 5328249 8/96 Remeron™ (mirtazapine) Tablets Manufactured for Organon Inc. West Orange, NJ 07052 USA by N.V. Organon, Oss, Holland 45 mg	NDC 0052-0100-90 5328249 8/96 Remeron™ (mirtazapine) Tablets Manufactured for Organon Inc. West Orange, NJ 07052 USA by N.V. Organon, Oss, Holland 45 mg	Lot Exp.
Exp. Lot	NDC 0052-0100-90 5328249 8/96 Remeron™ (mirtazapine) Tablets Manufactured for Organon Inc. West Orange, NJ 07052 USA by N.V. Organon, Oss, Holland 45 mg	NDC 0052-0100-90 5328249 8/96 Remeron™ (mirtazapine) Tablets Manufactured for Organon Inc. West Orange, NJ 07052 USA by N.V. Organon, Oss, Holland 45 mg	Lot Exp.

REMERON™ (mirtazapine) Tablets

45 mg

HOSPITAL UNIT DOSE
Bottle of 100 Carton

Manufactured for Organon Inc.
West Orange, NJ 07052 USA
by N.V. Organon, Oss, Holland



45 mg
REMERON™
(mirtazapine) Tablets

100 Tablets

HOSPITAL UNIT DOSE
NDC 0052-0109-90

NDC 0052-0109-90
HOSPITAL UNIT DOSE

100 Tablets

45 mg
REMERON™
(mirtazapine) Tablets



REMERON™
(mirtazapine) Tablets



100 Tablets

45 mg
REMERON™
(mirtazapine) Tablets



NDC 0052-0109-90
HOSPITAL UNIT DOSE

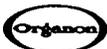
100 Tablets

45 mg
REMERON™
(mirtazapine) Tablets



Caution: Federal law prohibits dispensing without prescription.

Caution:
Federal law prohibits dispensing without prescription.



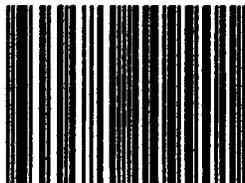
Manufactured for Organon Inc.
West Orange, NJ 07052 USA
by N.V. Organon, Oss, Holland



Manufactured for Organon Inc.
West Orange, NJ 07052 USA
by N.V. Organon, Oss, Holland



Manufactured for Organon Inc.
West Orange, NJ 07052 USA
by N.V. Organon, Oss, Holland



0299

REMERON™ (mirtazapine) Tablets

45 mg

HOSPITAL UNIT DOSE
Bottle of 100 Carton



Manufactured for Organon Inc.
West Orange, NJ 07052 USA
by N.V. Organon, Oss, Holland



REMERON™
45 mg
(mirtazapine) Tablets

100 Tablets

HOSPITAL UNIT DOSE
NDC 0052-0109-90



REMERON™
(mirtazapine) Tablets

100 Tablets



REMERON™
45 mg
(mirtazapine) Tablets



REMERON™
45 mg
(mirtazapine) Tablets

100 Tablets



REMERON™
45 mg
(mirtazapine) Tablets

NDC 0052-0109-90
HOSPITAL UNIT DOSE
100 Tablets



REMERON™
45 mg
(mirtazapine) Tablets

Caution: Federal law prohibits
dispensing without prescription.



Manufactured for Organon Inc.
West Orange, NJ 07052 USA
by N.V. Organon, Oss, Holland



REMERON™
45 mg
(mirtazapine) Tablets

Store at controlled room temperature 20°-25°C
(68°-77°F).

Each 45 mg tablet contains: 45 mg mirtazapine;
corn starch, NF; hydroxypropyl cellulose, NF;
magnesium stearate, NF; colloidal silicon dioxide,
NF; lactose, NF and other inactive ingredients.
Average Dose: Read enclosed prescribing
information.

Pkt. in USA 5315263

8/96



Manufactured for Organon Inc.
West Orange, NJ 07052 USA
by N.V. Organon, Oss, Holland