

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-208

FINAL PRINTED LABELING

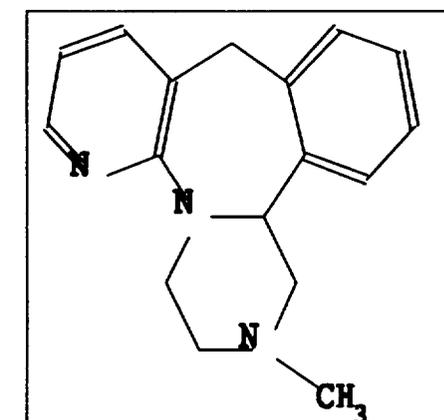
ATTACHMENT
NDA 21-208

[Note: Below is the Agency's final labeling for Remeron SolTab (mirtazapine) Orally Disintegrating Tablets. This labeling is identical to the most recently approved labeling for Remeron (mirtazapine) tablets (approved in an Agency letter dated August 30, 2000 for NDA 20-415/S-006) except for the highlighted revisions. All references to the Remeron (mirtazapine) tablets have been removed since the labeling for this new dosage form of mirtazapine will be a separate label. Double underline font denotes additions to the labeling, and strikethrough font denotes deletions to the labeling.]

REMERON[®] SolTab[™]
(mirtazapine) Orally Disintegrating Tablets

DESCRIPTION

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



STRUCTURAL FORMULA

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

water.

REMERON[®] SolTab[™] is available for oral administration as an orally disintegrating tablet containing 15, 30, or 45 mg of mirtazapine. It disintegrates in the mouth within seconds after placement on the tongue allowing its contents to be subsequently swallowed with or without water. REMERON[®] SolTab[™] also contains the following inactive ingredients: mannitol, granular mannitol, crospovidone, sodium bicarbonate, citric acid, microcrystalline cellulose, aspartame, magnesium stearate, and natural and artificial orange flavors.

CLINICAL PHARMACOLOGY

Pharmacodynamics

The mechanism of action of REMERON[®] SolTab[™] (mirtazapine) Orally Disintegrating Tablets, 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[®] SolTab[™] (mirtazapine) Orally Disintegrating Tablets are 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.

REMERON[®] SolTab[™] Orally Disintegrating Tablets are bioequivalent to REMERON[®] (mirtazapine) Tablets.

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

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

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

Special Populations

Geriatric

Following oral administration of REMERON® (mirtazapine) Tablets 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® SolTab™ (mirtazapine) Orally Disintegrating Tablets 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 20-40 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 REMERON® SolTab™.

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 = 11-39 mL/min/1.73m²) and approximately 50% in patients with severe (Clcr = <10 mL/min/1.73m²) renal impairment when compared to normal subjects. Caution is indicated in administering REMERON® SolTab™ to patients with compromised renal function (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Hepatic Insufficiency

Following a single 15 mg oral dose of REMERON®, 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® SolTab™ to patients with compromised hepatic function (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Clinical Trials Showing Effectiveness

The efficacy of REMERON® (mirtazapine) Tablets 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® SolTab™ (mirtazapine) Orally Disintegrating 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® SolTab™ in hospitalized depressed patients has not been adequately studied.

The effectiveness of REMERON® SolTab™ 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® SolTab™ for extended periods should periodically evaluate the long-term usefulness of the drug for the individual patient.

CONTRAINDICATIONS

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

WARNINGS

Agranulocytosis

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

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

Dizziness

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

Increased Appetite/Weight Gain

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

Cholesterol/Triglycerides

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

for placebo and 3% for amitriptyline.

Transaminase Elevations

Clinically significant ALT (SGPT) elevations ≥ 3 times the upper limit of the normal range) were observed in 2.0% (8/424) of patients exposed to REMERON[®] in a pool of short-term 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. REMERON[®] SolTab[™] 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 REMERON[®] 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[®]. 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[®] SolTab[™] 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[®] SolTab[™] 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.

REMERON[®] SolTab[™] 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.

REMERON[®] 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[®] SolTab[™] 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. Caution is indicated in administering REMERON[®] SolTab[™] 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 REMERON[®] SolTab[™] (mirtazapine) Orally Disintegrating Tablets.

Agranulocytosis

Patients who are to receive REMERON[®] SolTab[™] 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[®] SolTab[™] 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[®] SolTab[™] therapy does not adversely affect their ability to engage in such activities.

Completing Course of Therapy

While patients may notice improvement with REMERON[®] SolTab[™] 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[®] SolTab[™] to interact with other drugs.

Alcohol

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

Pregnancy

Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during REMERON® SolTab™ 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® SolTab™ (mirtazapine) Orally Disintegrating 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 REMERON® SolTab™ 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 REMERON® SolTab™ with such drugs.

Alcohol

Concomitant administration of alcohol (equivalent to 60 g) had a minimal effect on plasma levels of mirtazapine (15mg) in 6 healthy male subjects. However, the impairment of

cognitive and motor skills produced by REMERON[®] were shown to be additive with those produced by alcohol. Accordingly, patients should be advised to avoid alcohol while taking REMERON[®] SolTab[™].

Diazepam

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

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

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

The doses used in the mouse study may not have been high enough to fully characterize the carcinogenic potential of REMERON[®] (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/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 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. The effects occurred at doses that were 20 times the MRHD, but not at 3 times the MRHD, on a mg/m² basis. There are no adequate and well controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers

It is not known whether mirtazapine is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when REMERON[®] SolTab[™] (mirtazapine) Orally Disintegrating 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) 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 REMERON[®] SolTab[™] (mirtazapine) Orally Disintegrating Tablets 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) 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. 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) Tablets (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) 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.

**APPEARS THIS WAY
ON ORIGINAL**

**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[®] are included, except the following

events which had an incidence on placebo \geq 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

The electrocardiograms for 338 patients who received REMERON[®] 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 REMERON[®]

During its premarketing assessment, multiple doses of REMERON[®] (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 REMERON[®] who experienced an event of the type cited on at least one occasion while receiving REMERON[®]. All reported events are included except those already listed in the previous table, those adverse experiences subsumed under COSTART terms that are either overly general or excessively specific so as to be uninformative, and those events for which a drug cause was very remote.

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

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

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

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

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

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

Endocrine System *rare:* goiter, hypothyroidism.

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

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

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

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

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

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

seborrhea, skin ulcer.

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

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

Other Adverse Events Observed During Postmarketing Evaluation of REMERON

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

DRUG ABUSE AND DEPENDENCE

Controlled Substance Class

REMERON[®] SolTab™ (mirtazapine) Orally Disintegrating Tablets are not a controlled substance.

Physical and Psychological Dependence

REMERON[®] SolTab™ (mirtazapine) Orally Disintegrating(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 REMERON[®] SolTab™ misuse or abuse (e.g., development of tolerance, incrementations of dose, drug-seeking behavior).

OVERDOSAGE

Human Experience

There is very limited experience with REMERON[®] SolTab™ (mirtazapine) Orally Disintegrating Tablets overdose. In premarketing clinical studies, there

were eight reports of REMERON[®] overdose alone or in combination with other pharmacological agents. The only drug overdose death reported while taking REMERON[®] 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. 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. Because of the rapid disintegration of Remeron Soltab tablets, pill fragments may not appear in gastric contents obtained with lavage.

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 *Physician's Desk Reference* (PDR).

DOSAGE AND ADMINISTRATION

Initial Treatment

The recommended starting dose for REMERON[®] SolTab™ (mirtazapine) Orally Disintegrating Tablets 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.

Administration of REMERON[®] SolTab[™] (mirtazapine) Orally Disintegrating Tablets

Patients should be instructed to open the tablet blister pack with dry hands and place the tablet on the tongue. The tablet should be used immediately after removal from its blister; once removed, it cannot be stored. REMERON[®] SolTab[™] (mirtazapine) Orally Disintegrating Tablet will disintegrate rapidly on the tongue and can be swallowed with saliva. No water is needed for taking the tablet. Patients should not attempt to split the tablet.

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

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

Switching Patients To or From a Monoamine Oxidase Inhibitor

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

HOW SUPPLIED

REMERON[®] SolTab[™] (mirtazapine) Orally Disintegrating Tablets are supplied as:

15 mg Tablets - round, white, with "1^T Z" debossed on one side.

Box of 30 5 x 6 Unit Dose Blisters NDC 0052-0106-30

Box of 90 15 x 6 Unit Dose Blisters NDC 0052-0106-90

30 mg Tablets - round, white with "2^T Z" debossed on one side.

Box of 30 5 x 6 Unit Dose Blisters NDC 0052-0108-30

Box of 90 15 x 6 Unit Dose Blisters NDC 0052-0108-90

45 mg Tablets - round, white with "T₄Z" debossed on one side.

Box of 30 5 x 6 Unit Dose Blisters _____ NDC 0052-0110-30

Box of 90 15 x 6 Unit Dose Blisters _____ NDC 0052-0110-90

Storage

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. Use immediately upon opening individual tablet blister.

R only



REMERON® SolTab™ (mirtazapine) Orally Disintegrating Tablets

Manufactured for Organon Inc.

West Orange, NJ 07052

by CIMA Labs Inc.

Eden Prairie, MN 55344

/s/

Russell Katz
1/12/01 07:51:32 AM

**APPEARS THIS WAY
ON ORIGINAL**