

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use REMERON/REMERONSolTab safely and effectively. See full prescribing information for REMERON/REMERONSolTab.

REMERON® (mirtazapine) tablets, for oral use
REMERONSolTab® (mirtazapine) orally disintegrating tablets
Initial U.S. Approval: 1996

WARNING: SUICIDAL THOUGHTS AND BEHAVIORS See full prescribing information for complete boxed warning.

Increased risk of suicidal thoughts and behavior in pediatric and young adult patients taking antidepressants. Closely monitor all antidepressant-treated patients for clinical worsening and emergence of suicidal thoughts and behaviors.
REMERON/REMERONSolTab is not approved for use in pediatric patients. (5.1, 8.4)

INDICATIONS AND USAGE

REMERON/REMERONSolTab is indicated for the treatment of major depressive disorder (MDD) in adults. (1)

DOSAGE AND ADMINISTRATION

- Starting dose: 15-mg once daily; may increase up to maximum recommended dose of 45 mg once daily. (2.1)
- Administer orally once daily, preferably in the evening prior to sleep. (2.1)
- Administer REMERONSolTab immediately after removal from blister pack. (2.2)
- Reduce dose gradually when discontinuing REMERON/REMERONSolTab. (2.6, 5.13)

DOSAGE FORMS AND STRENGTHS

- Tablets: 15 mg scored and 30 mg scored. (3)
- Orally disintegrating tablets: 15 mg, 30 mg, and 45 mg. (3)

CONTRAINDICATIONS

- Concomitant use of monoamine oxidase inhibitors (MAOIs) or use within 14 days of stopping MAOIs. (2.4, 4, 7)
- Known hypersensitivity to mirtazapine or any of the excipients in REMERON/REMERONSolTab. (4)

WARNINGS AND PRECAUTIONS

- Agranulocytosis:** If sore throat, fever, stomatitis or signs of infection occur, along with a low white blood cell count, treatment with REMERON/REMERONSolTab should be discontinued and the patient should be closely monitored. (5.2)
- Serotonin Syndrome:** Increased risk when co-administered with other serotonergic drugs (e.g., SSRI, SNRI, triptans), but also when taken alone. If it occurs, discontinue REMERON/REMERONSolTab and initiate supportive treatment. (2.4, 4, 5.3, 7)
- Angle-Closure Glaucoma:** Angle closure glaucoma has occurred in patients with untreated anatomically narrow angles treated with antidepressants. (5.4)

- QT Prolongation:** Use REMERON/REMERONSolTab with caution in patients with risk factors for QT prolongation. (5.5, 7)
- Increased Appetite/Weight Gain:** REMERON/REMERONSolTab has been associated with increased appetite and weight gain. (5.6)
- Somnolence:** May impair judgment, thinking and/or motor skills. Use with caution when engaging in activities requiring alertness, such as driving or operating machinery. (5.7, 7)
- Activation of Mania/Hypomania:** Screen patients for bipolar disorder prior to initiating treatment. (2.3, 5.8)
- Seizures:** Use with caution in patients with a seizure disorder. (5.9)
- Elevated Cholesterol/Triglycerides:** Has been reported with REMERON use. (5.10)
- Hyponatremia:** May occur as a result of treatment with serotonergic antidepressants, including REMERON/REMERONSolTab. (5.11)
- Transaminase Elevations:** Clinically significant elevations have occurred. Use with caution in patients with impaired hepatic function. (5.12)

ADVERSE REACTIONS

Most common adverse reactions (≥5% or greater and twice placebo) were somnolence, increased appetite, weight gain, and dizziness. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Organon USA LLC, a subsidiary of Organon & Co., at 1-844-674-3200 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Strong CYP3A inducers:** Dosage increase may be needed for REMERON/REMERONSolTab with concomitant use of strong CYP3A inducers. (2.5, 7)
- Strong CYP3A inhibitors:** Dosage decrease may be needed when REMERON/REMERONSolTab is coadministered with strong CYP3A inhibitors. (2.5, 7)
- Cimetidine:** Dosage decrease may be needed when REMERON/REMERONSolTab is coadministered with cimetidine. (2.5, 7)
- Warfarin:** Monitor INR during concomitant use. (7)

USE IN SPECIFIC POPULATIONS

- Geriatric Use:** Use with caution in elderly patients. (5.11, 5.14, 8.5)
- Renal impairment:** Dosage decrease may be needed in patients with moderate to severe renal impairment. (8.6)
- Hepatic impairment:** Dosage decrease may be needed in patients with hepatic impairment. (8.6)
- Patients with Phenylketonuria:** REMERONSolTab contains phenylalanine. (5.15, 8.7)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

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FULL PRESCRIBING INFORMATION

WARNING: SUICIDAL THOUGHTS AND BEHAVIORS

Antidepressants increased the risk of suicidal thoughts and behaviors in pediatric and young adult patients in short-term studies. Closely monitor all antidepressant-treated patients for clinical worsening, and for emergence of suicidal thoughts and behaviors [see *Warnings and Precautions (5.1)*]. REMERON/REMERONSolTab is not approved for use in pediatric patients [see *Use in Specific Populations (8.4)*].

1 INDICATIONS AND USAGE

REMERON/REMERONSolTab are indicated for the treatment of major depressive disorder (MDD) in adults [see *Clinical Studies (14)*].

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

The recommended starting dose of REMERON/REMERONSolTab is 15 mg once daily, administered orally, preferably in the evening prior to sleep. If patients do not have an adequate response to the initial 15 mg dose, increase the dose up to a maximum of 45 mg per day. Dose changes should not be made in intervals of less than 1 to 2 weeks to allow sufficient time for evaluation of response to a given dose [see *Clinical Pharmacology (12.3)*].

2.2 Administration of REMERONSolTab

- The tablet should remain in the blister pack until the patient is ready to take it.
- The patient or caregiver should use dry hands to open the blister.
- As soon as the blister is opened, the tablet should be removed and placed on the patient's tongue.
- Use REMERONSolTab immediately after removal from its blister; once removed, it cannot be stored.
- The whole tablet should be placed on the tongue and allowed to disintegrate without chewing or crushing. Do not attempt to split the tablet.
- The tablet will disintegrate in saliva so that it can be swallowed.

2.3 Screen for Bipolar Disorder Prior to Starting REMERON/REMERONSolTab

Prior to initiating treatment with REMERON/REMERONSolTab or another antidepressant, screen patients for a personal or family history of bipolar disorder, mania, or hypomania [see *Warnings and Precautions (5.8)*].

2.4 Switching Patients to or from a Monoamine Oxidase Inhibitor Antidepressant

At least 14 days must elapse between discontinuation of a monoamine oxidase inhibitor (MAOI) antidepressant and initiation of REMERON/REMERONSolTab. In addition, at least 14 days must elapse after stopping REMERON/REMERONSolTab before starting an MAOI antidepressant [see *Contraindications (4) and Warnings and Precautions (5.3)*].

2.5 Dosage Modifications Due to Drug Interactions

Strong CYP3A Inducers

An increase in dosage of REMERON/REMERONSolTab may be needed with concomitant strong CYP3A inducer (e.g., carbamazepine, phenytoin, rifampin) use. Conversely, a decrease in dosage of REMERON/REMERONSolTab may be needed if the CYP3A inducer is discontinued [see *Drug Interactions (7)*].

Strong CYP3A Inhibitors

A decrease in dosage of REMERON/REMERONSolTab may be needed with concomitant use of strong CYP3A4 inhibitors (e.g., ketoconazole, clarithromycin). Conversely, an increase in dosage of

REMERON/REMERONSolTab may be needed if the CYP3A4 inhibitor is discontinued [see *Drug Interactions (7)*].

Cimetidine

A decrease in dosage of REMERON/REMERONSolTab may be needed with concomitant use of cimetidine. Conversely, an increase in dosage of REMERON/REMERONSolTab may be needed if cimetidine is discontinued [see *Drug Interactions (7)*].

2.6 Discontinuation of REMERON/REMERONSolTab Treatment

Adverse reactions may occur upon discontinuation or dose reduction of REMERON/REMERONSolTab [see *Warnings and Precautions (5.13)*]. Gradually reduce the dosage of REMERON/REMERONSolTab rather than stopping abruptly whenever possible.

3 DOSAGE FORMS AND STRENGTHS

REMERON is supplied as:

- 15 mg tablets: Oval, scored, yellow, with "MSD" debossed on one side and "T₃Z" on the other side, on both sides of the score line
- 30 mg tablets: Oval, scored, red-brown, with "MSD" debossed on one side and "T₅Z" on the other side, on both sides of the score line

REMERONSolTab is supplied as:

- 15 mg orally disintegrating tablets: Round, white, with "T₁Z" debossed on one side
- 30 mg orally disintegrating tablets: Round, white, with "T₂Z" debossed on one side
- 45 mg orally disintegrating tablets: Round, white, with "T₄Z" debossed on one side

4 CONTRAINDICATIONS

REMERON/REMERONSolTab is contraindicated in patients:

- Taking, or within 14 days of stopping, MAOIs (including the MAOIs linezolid and intravenous methylene blue) because of an increased risk of serotonin syndrome [see *Warnings and Precautions (5.3)*, *Drug Interactions (7)*].
- With a known hypersensitivity to mirtazapine or to any of the excipients in REMERON/REMERONSolTab. Severe skin reactions, including Stevens-Johnson syndrome, bullous dermatitis, erythema multiforme and toxic epidermal necrolysis have been reported following the use of REMERON/REMERONSolTab [see *Adverse Reactions 6.2*].

5 WARNINGS AND PRECAUTIONS

5.1 Suicidal Thoughts and Behaviors in Adolescents and Young Adults

In pooled analyses of placebo-controlled trials of antidepressant drugs (SSRIs and other antidepressant classes) that included approximately 77,000 adult patients and 4,500 pediatric patients, the incidence of suicidal thoughts and behaviors in antidepressant-treated patients age 24 years and younger was greater than in placebo-treated patients. There was considerable variation in risk of suicidal thoughts and behaviors among drugs, but there was an increased risk identified in young patients for most drugs studied. There were differences in absolute risk of suicidal thoughts and behaviors across the different indications, with the highest incidence in patients with MDD. The drug-placebo differences in the number of cases of suicidal thoughts and behaviors per 1000 patients treated are provided in Table 1.

Table 1: Risk Differences of the Number of Patients with Suicidal Thoughts and Behavior in the Pooled Placebo-Controlled Trials of Antidepressants in Pediatric and Adult Patients

Age Range	Drug-Placebo Difference in Number of Patients with Suicidal Thoughts or Behaviors per 1000 Patients Treated
	Increases Compared to Placebo
<18 years old	14 additional patients
18–24 years old	5 additional patients
	Decreases Compared to Placebo
25–64 years old	1 fewer patient
≥65 years old	6 fewer patients

It is unknown whether the risk of suicidal thoughts and behaviors in children, adolescents, and young adults extends to longer-term use, i.e., beyond four months. However, there is substantial evidence from placebo-controlled maintenance trials in adults with MDD that antidepressants delay the recurrence of depression and that depression itself is a risk factor for suicidal thoughts and behaviors.

Monitor all antidepressant-treated patients for any indication of clinical worsening and emergence of suicidal thoughts and behaviors, especially during the initial few months of drug therapy, and at times of dosage changes. Counsel family members or caregivers of patients to monitor for changes in behavior and to alert the healthcare provider. Consider changing the therapeutic regimen, including possibly discontinuing REMERON/REMERONSolTab, in patients whose depression is persistently worse, or who are experiencing emergent suicidal thoughts or behaviors.

5.2 Agranulocytosis

In premarketing clinical trials, 2 (1 with Sjögren’s Syndrome) out of 2796 patients treated with REMERON 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 3 patients, onset of severe neutropenia was detected on days 61, 9, and 14 of treatment, respectively. All 3 patients recovered after REMERON was stopped. If a patient develops a sore throat, fever, stomatitis, or other signs of infection, along with a low white blood cell (WBC) count, treatment with REMERON/REMERONSolTab should be discontinued and the patient should be closely monitored.

5.3 Serotonin Syndrome

Serotonergic antidepressants, including REMERON/REMERONSolTab, can precipitate serotonin syndrome, a potentially life-threatening condition. The risk is increased with concomitant use of other serotonergic drugs (including triptans, tricyclic antidepressants, fentanyl, lithium, tramadol, tryptophan, buspirone, amphetamines, and St. John’s Wort) and with drugs that impair metabolism of serotonin, i.e., MAOIs [see *Contraindications (4)*, *Drug Interactions (7)*]. Serotonin syndrome can also occur when these drugs are used alone.

Serotonin syndrome signs and symptoms may include mental status changes (e.g., agitation, hallucinations, delirium, and coma), autonomic instability (e.g., tachycardia, labile blood pressure, dizziness, diaphoresis, flushing, hyperthermia), neuromuscular symptoms (e.g., tremor, rigidity, myoclonus, hyperreflexia, incoordination), seizures, and gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea).

The concomitant use of REMERON/REMERONSolTab with MAOIs is contraindicated. In addition, do not initiate REMERON/REMERONSolTab in a patient being treated with MAOIs such as linezolid or intravenous methylene blue. No reports involved the administration of methylene blue by other routes (such as oral tablets or local tissue injection). If it is necessary to initiate treatment with an MAOI such as linezolid or intravenous methylene blue in a patient taking REMERON/REMERONSolTab, discontinue

REMERON/REMERONSoITab before initiating treatment with the MAOI [see *Contraindications (4), Drug Interactions (7)*].

Monitor all patients taking REMERON/REMERONSoITab for the emergence of serotonin syndrome. Discontinue treatment with REMERON/REMERONSoITab and any concomitant serotonergic agents immediately if the above symptoms occur, and initiate supportive symptomatic treatment. If concomitant use of REMERON/REMERONSoITab with other serotonergic drugs is clinically warranted, inform patients of the increased risk for serotonin syndrome and monitor for symptoms.

5.4 Angle-Closure Glaucoma

The pupillary dilation that occurs following use of many antidepressant drugs, including REMERON/REMERONSoITab, may trigger an angle-closure attack in a patient with anatomically narrow angles who does not have a patent iridectomy.

5.5 QT Prolongation and Torsades de Pointes

The effect of REMERON (mirtazapine) on QTc interval was assessed in a clinical randomized trial with placebo and positive (moxifloxacin) controls involving 54 healthy volunteers using exposure response analysis. This trial showed a positive relationship between mirtazapine concentrations and prolongation of the QTc interval. However, the degree of QT prolongation observed with both 45 mg and 75 mg (1.67 times the maximum recommended daily dose) doses of mirtazapine was not at a level generally considered to be clinically meaningful. During postmarketing use of mirtazapine, cases of QT prolongation, Torsades de Pointes, ventricular tachycardia, and sudden death, have been reported [see *Adverse Reactions (6.1, 6.2)*]. The majority of reports occurred in association with overdose or in patients with other risk factors for QT prolongation, including concomitant use of QTc-prolonging medicines [see *Drug Interactions (7) and Overdosage (10)*]. Exercise caution when REMERON/REMERONSoITab is prescribed in patients with known cardiovascular disease or family history of QT prolongation, and in concomitant use with other drugs thought to prolong the QTc interval.

5.6 Increased Appetite and Weight Gain

In U.S. controlled clinical studies, appetite increase was reported in 17% of patients treated with REMERON, compared to 2% for placebo. 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. In a pool of premarketing U.S. clinical studies, including many patients for long-term, open-label treatment, 8% of patients receiving REMERON discontinued for weight gain.

In an 8-week-long pediatric clinical trial of doses between 15 to 45 mg/day, 49% of REMERON-treated pediatric patients had a weight gain of at least 7%, compared to 5.7% of placebo-treated patients. The safety and effectiveness of REMERON/REMERONSoITab in pediatric patients with MDD have not been established [see *Use in Specific Populations (8.4)*].

5.7 Somnolence

In U.S. controlled studies, somnolence was reported in 54% of patients treated with REMERON, compared to 18% for placebo. In these studies, somnolence resulted in discontinuation for 10.4% of REMERON-treated patients, compared to 2.2% for placebo. It is unclear whether tolerance develops to the somnolent effects of REMERON/REMERONSoITab. Because of the potentially significant effects of REMERON/REMERONSoITab on impairment of performance, caution patients about engaging in activities that require alertness, including operating hazardous machinery and motor vehicles, until they are reasonably certain that REMERON/REMERONSoITab does not affect them adversely. The concomitant use of benzodiazepines and alcohol with REMERON/REMERONSoITab should be avoided [see *Drug Interactions (7)*].

5.8 Activation of Mania or Hypomania

In patients with bipolar disorder, treating a depressive episode with REMERON/REMERONSoITab or another antidepressant may precipitate a mixed/manic episode. In controlled clinical trials, patients with bipolar disorder were generally excluded; however, symptoms of mania or hypomania were reported in

0.2% of patients treated with REMERON. Prior to initiating treatment with REMERON/REMERONSolTab, screen patients for any personal or family history of bipolar disorder, mania, or hypomania.

5.9 Seizures

REMERON/REMERONSolTab has not been systematically evaluated in patients with seizure disorders. In premarketing clinical trials, 1 seizure was reported among the 2796 U.S. and non-U.S. patients treated with REMERON. REMERON/REMERONSolTab should be prescribed with caution in patients with a seizure disorder.

5.10 Elevated Cholesterol and 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. In these same studies, nonfasting triglyceride increases to ≥ 500 mg/dL were observed in 6% of patients treated with REMERON, compared to 3% for placebo.

5.11 Hyponatremia

Hyponatremia may occur as a result of treatment with serotonergic antidepressants, including REMERON/REMERONSolTab. Cases with serum sodium lower than 110 mmol/L have been reported.

Signs and symptoms of hyponatremia include headache, difficulty concentrating, memory impairment, confusion, weakness, and unsteadiness, which may lead to falls. Signs and symptoms associated with more severe or acute cases have included hallucination, syncope, seizure, coma, respiratory arrest, and death. In many cases, this hyponatremia appears to be the result of the syndrome of inappropriate antidiuretic hormone secretion (SIADH).

In patients with symptomatic hyponatremia, discontinue REMERON/REMERONSolTab and institute appropriate medical intervention. Elderly patients, patients taking diuretics, and those who are volume-depleted may be at greater risk of developing hyponatremia [see *Use in Specific Populations (8.5)*].

5.12 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 treated with REMERON in a pool of short-term, U.S. controlled trials, compared to 0.3% (1/328) of placebo patients. While some patients were discontinued for the ALT increases, in other cases, the enzyme levels returned to normal despite continued REMERON treatment. REMERON/REMERONSolTab should be used with caution in patients with impaired hepatic function [see *Use in Specific Populations (8.6)*, *Clinical Pharmacology (12.3)*].

5.13 Discontinuation Syndrome

There have been reports of adverse reactions upon the discontinuation of REMERON/REMERONSolTab (particularly when abrupt), including but not limited to the following: dizziness, abnormal dreams, sensory disturbances (including paresthesia and electric shock sensations), agitation, anxiety, fatigue, confusion, headache, tremor, nausea, vomiting, and sweating, or other symptoms which may be of clinical significance.

A gradual reduction in the dosage, rather than an abrupt cessation, is recommended [see *Dosage and Administration (2.6)*].

5.14 Use in Patients with Concomitant Illness

REMERON/REMERONSolTab 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 [see *Adverse Reactions (6.1)*]. REMERON/REMERONSolTab 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).

5.15 Risks in Patients with Phenylketonuria

Phenylalanine can be harmful to patients with phenylketonuria (PKU). REMERONSolTab contains phenylalanine, a component of aspartame. REMERONSolTab contains the following amount of phenylalanine: 2.6 mg in 15 mg orally disintegrating tablet, 5.2 mg in 30 mg orally disintegrating tablet, and 7.8 mg in 45 mg orally disintegrating tablet. Before prescribing REMERONSolTab to a patient with PKU, consider the combined daily amount of phenylalanine from all sources, including REMERONSolTab.

6 ADVERSE REACTIONS

The following adverse reactions are described in more detail in other sections of the prescribing information:

- Hypersensitivity [see *Contraindications (4)*]
- Suicidal Thoughts and Behaviors [see *Warnings and Precautions (5.1)*]
- Agranulocytosis [see *Warnings and Precautions (5.2)*]
- Serotonin Syndrome [see *Contraindications (4)*, *Warnings and Precautions (5.3)*, *Drug Interactions (7)*]
- Angle-Closure Glaucoma [see *Warnings and Precautions (5.4)*]
- QT Prolongation and Torsades de Pointes [see *Warnings and Precautions (5.5)*]
- Increased Appetite and Weight Gain [see *Warnings and Precautions (5.6)*]
- Somnolence [see *Warnings and Precautions (5.7)*]
- Activation of Mania or Hypomania [see *Warnings and Precautions (5.8)*]
- Seizures [see *Warnings and Precautions (5.9)*]
- Elevated Cholesterol and Triglycerides [see *Warnings and Precautions (5.10)*]
- Hyponatremia [see *Warnings and Precautions (5.11)*]
- Transaminase Elevations [see *Warnings and Precautions (5.12)*]
- Discontinuation Syndrome [see *Warnings and Precautions (5.13)*]
- Use in Patients with Concomitant Illness [see *Warnings and Precautions (5.14)*]

6.1 Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The data described below are from clinical trials in which REMERON/REMERONSolTab was administered to 2796 patients in phase 2 and 3 clinical studies. The trials consisted of double-blind controlled and open-label studies, inpatient and outpatient studies, fixed dose, and titration studies.

Adverse Reactions Leading to Discontinuation of Treatment

Approximately 16% of the 453 patients who received REMERON in U.S. 6-week placebo-controlled clinical trials discontinued treatment due to an adverse reaction, compared to 7% of the 361 placebo-treated patients in those studies. The most common reactions leading to discontinuation ($\geq 1\%$ and at a rate at least twice that of placebo) are included in Table 2.

Table 2: Adverse Reactions ($\geq 1\%$ and at least twice placebo) Leading to Discontinuation of REMERON in 6-Week Clinical Trials in Patients with MDD

	REMERON (n=453)	Placebo (n=361)
Somnolence	10.4%	2.2%
Nausea	1.5%	0%

Common Adverse Reactions

The most common adverse reactions ($\geq 5\%$ and twice placebo) associated with the use of REMERON are listed in Table 3.

Table 3: Adverse Reactions ($\geq 5\%$ and twice placebo) in 6-Week U.S. Clinical Trials of REMERON in Patients with MDD

	REMERON (n=453)	Placebo (n=361)
Somnolence	54%	18%
Increased Appetite	17%	2%
Weight Gain	12%	2%
Dizziness	7%	3%

Table 4 enumerates adverse reactions that occurred in $\geq 1\%$ of REMERON-treated patients, and were more frequent than the placebo-treated patients, who participated in 6-week, 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 1 episode of an adverse reaction at some time during their treatment.

Table 4: Adverse Reactions ($\geq 1\%$ and greater than placebo) in 6-Week U.S. Clinical Studies of Remeron in Patients with MDD

	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%

ECG Changes

The electrocardiograms for 338 patients who received REMERON and 261 patients who received placebo in 6-week, placebo-controlled trials were analyzed. REMERON 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 Reactions Observed During the Premarketing Evaluation of REMERON

The following list does not include reactions: 1) already listed in previous tables or elsewhere in labeling, 2) for which a drug cause was remote, 3) which were so general or excessively specific so as to be uninformative, 4) which were not considered to have significant clinical implications, or 5) which occurred at a rate equal to or less than placebo.

Adverse reactions are categorized by body system according to the following definitions: *frequent* adverse reactions are those occurring in at least 1/100 patients; *infrequent* adverse reactions are those occurring in 1/100 to 1/1000 patients; *rare* adverse reactions are those occurring in fewer than 1/1000 patients.

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, hyponatremia.

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 (psychomotor restlessness), stupor, dementia, diplopia, drug dependence, paralysis, grand mal convulsion, hypotonia, myoclonus, psychotic depression, withdrawal syndrome, serotonin 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, angle-closure 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.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of REMERON. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Cardiac disorders: ventricular arrhythmia (Torsades de Pointes)

Endocrine disorders: hyperprolactinemia (and related symptoms, e.g., galactorrhea and gynecomastia)

Musculoskeletal and connective tissue disorders: increased creatine kinase blood levels and rhabdomyolysis

Psychiatric disorders: somnambulism (ambulation and other complex behaviors out of bed)

Reproductive system and breast disorders: priapism

Skin and subcutaneous tissue disorders: severe skin reactions, including Stevens-Johnson syndrome, bullous dermatitis, erythema multiforme and toxic epidermal necrolysis

7 DRUG INTERACTIONS

Table 5 includes clinically important drug interactions with REMERON/REMERONSolTab [see *Clinical Pharmacology* (12.3)].

Table 5: Clinically Important Drug Interactions with REMERON/REMERONSolTab

Monoamine Oxidase Inhibitors (MAOIs)	
<i>Clinical Impact</i>	The concomitant use of serotonergic drugs, including REMERON/REMERONSolTab, and MAOIs increases the risk of serotonin syndrome.
<i>Intervention</i>	REMERON/REMERONSolTab is contraindicated in patients taking MAOIs, including MAOIs such as linezolid or intravenous methylene blue [see <i>Dosage and Administration (2.4)</i> , <i>Contraindications (4)</i> , <i>Warnings and Precautions (5.3)</i>].
<i>Examples</i>	selegiline, tranylcypromine, isocarboxazid, phenelzine, linezolid, methylene blue
Other Serotonergic Drugs	
<i>Clinical Impact</i>	The concomitant use of serotonergic drugs with REMERON/REMERONSolTab increases the risk of serotonin syndrome.
<i>Intervention</i>	Monitor patients for signs and symptoms of serotonin syndrome, particularly during treatment initiation and dosage increases. If serotonin syndrome occurs, consider discontinuation of REMERON/REMERONSolTab and/or concomitant serotonergic drugs [see <i>Warnings and Precautions (5.3)</i>].
<i>Examples</i>	SSRIs, SNRIs, triptans, tricyclic antidepressants, fentanyl, lithium, amphetamines, St. John's Wort, tramadol, tryptophan, buspirone
Strong CYP3A Inducers	
<i>Clinical Impact</i>	The concomitant use of strong CYP3A inducers with REMERON/REMERONSolTab decreases the plasma concentration of mirtazapine [see <i>Clinical Pharmacology (12.3)</i>].
<i>Intervention</i>	Increase the dose of REMERON/REMERONSolTab if needed with concomitant CYP3A inducer use. Conversely, a decrease in dosage of REMERON/REMERONSolTab may be needed if the CYP3A inducer is discontinued [see <i>Dosage and Administration (2.5)</i>].
<i>Examples</i>	phenytoin, carbamazepine, rifampin
Strong CYP3A Inhibitors	
<i>Clinical Impact</i>	The concomitant use of strong CYP3A inhibitors with REMERON/REMERONSolTab may increase the plasma concentration of mirtazapine [see <i>Clinical Pharmacology (12.3)</i>].
<i>Intervention</i>	Decrease the dose of REMERON/REMERONSolTab if needed with concomitant strong CYP3A inhibitor use. Conversely, an increase in dosage of REMERON/REMERONSolTab may be needed if the CYP3A inhibitor is discontinued [see <i>Dosage and Administration (2.5)</i>].
<i>Examples</i>	itraconazole, ritonavir, nefazodone
Cimetidine	
<i>Clinical Impact</i>	The concomitant use of cimetidine, a CYP1A2, CYP2D6, and CYP3A inhibitor, with REMERON/REMERONSolTab may increase the plasma concentration of mirtazapine [see <i>Clinical Pharmacology (12.3)</i>].
<i>Intervention</i>	Decrease the dose of REMERON/REMERONSolTab if needed with concomitant cimetidine use. Conversely, an increase in dosage of REMERON/REMERONSolTab may be needed if cimetidine is discontinued [see <i>Dosage and Administration (2.5)</i>].
Benzodiazepines and Alcohol	

<i>Clinical Impact</i>	The concomitant use of benzodiazepines or alcohol with REMERON/REMERONSoI Tab increases the impairment of cognitive and motor skills produced by REMERON/REMERONSoI Tab alone.
<i>Intervention</i>	Avoid concomitant use of benzodiazepines and alcohol with REMERON/REMERONSoI Tab [see <i>Warnings and Precautions (5.7)</i> , <i>Clinical Pharmacology (12.3)</i>].
<i>Examples</i>	diazepam, alprazolam, alcohol
Drugs that Prolong QTc Interval	
<i>Clinical Impact</i>	The concomitant use of other drugs which prolong the QTc interval with REMERON/REMERONSoI Tab, increase the risk of QT prolongation and/or ventricular arrhythmias (e.g., Torsades de Pointes).
<i>Intervention</i>	Use caution when using REMERON/REMERONSoI Tab concomitantly with drugs that prolong the QTc interval [see <i>Warnings and Precautions (5.5)</i> , <i>Clinical Pharmacology (12.3)</i>].
Warfarin	
<i>Clinical Impact</i>	The concomitant use of warfarin with REMERON/REMERONSoI Tab may result in an increase in INR [see <i>Clinical Pharmacology (12.3)</i>].
<i>Intervention</i>	Monitor INR during concomitant use of warfarin with REMERON/REMERONSoI Tab.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to antidepressants during pregnancy. Healthcare providers are encouraged to register patients by calling the National Pregnancy Registry for Antidepressants at 1-844-405-6185 or visiting online at <https://womensmentalhealth.org/clinical-and-research-programs/pregnancyregistry/antidepressants/>.

Risk Summary

Prolonged experience with mirtazapine in pregnant women, based on published observational studies and postmarketing reports, has not reliably identified a drug-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. There are risks associated with untreated depression in pregnancy (see *Clinical Considerations*).

In animal reproduction studies, oral administration of mirtazapine to pregnant rats and rabbits during the period of organogenesis revealed no evidence of teratogenic effects up to 20 and 17 times the maximum recommended human dose (MRHD) of 45 mg, respectively, based on mg/m² body surface area. However, in rats, there was an increase in postimplantation loss at 20 times the MRHD based on mg/m² body surface area. Oral administration of mirtazapine to pregnant rats during pregnancy and lactation resulted in an increase in pup deaths and a decrease in pup birth weights at doses 20 times the MRHD based on mg/m² body surface area (see *Data*).

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Clinical Considerations

Disease-Associated Maternal and/or Embryo/Fetal Risk

Women who discontinue antidepressants during pregnancy are more likely to experience a relapse of major depression than women who continue antidepressants. This finding is from a prospective,

longitudinal study that followed 201 pregnant women with a history of major depressive disorder who were euthymic and taking antidepressants at the beginning of pregnancy. Consider the risk of untreated depression when discontinuing or changing treatment with antidepressant medication during pregnancy and postpartum.

Data

Animal Data

Mirtazapine was administered orally to pregnant rats and rabbits during the period of organogenesis at doses of 2.5, 15, and 100 mg/kg/day and 2.5, 10, and 40 mg/kg/day, respectively, which are up to 20 and 17 times the maximum recommended human dose (MRHD) of 45 mg based on mg/m² body surface area, respectively. No evidence of teratogenic effects was observed. However, in rats, there was an increase in postimplantation loss in dams treated with mirtazapine at 100 mg/kg/day which is 20 times the MRHD based on mg/m² body surface area. Oral administration of mirtazapine at doses of 2.5, 15, and 100 mg/kg/day to pregnant rats during pregnancy and lactation resulted in an increase in pup deaths during the first 3 days of lactation and a decrease in pup birth weights at 20 times the MRHD based on mg/m² body surface area. The cause of these deaths is not known. The no effect dose level is 3 times the MRHD based on mg/m² body surface area.

8.2 Lactation

Risk Summary

Data from published literature report the presence of mirtazapine in human milk at low levels with relative infant doses for mirtazapine ranging between 0.6 and 2.8% of the maternal weight-adjusted dose (see *Data*). No adverse effects on the breastfed infant have been reported in most cases of maternal use of mirtazapine. There are no data on the effects of mirtazapine on milk production.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for mirtazapine and any potential adverse effects on the breastfed infant from mirtazapine or from the underlying maternal condition.

Data

In a published pooled analysis of 8 breastfeeding mother-infant pairs, the mean (min, max) total relative infant doses for mirtazapine and its desmethyl metabolite were 1.5% (0.6%, 2.8%) and 0.4% (0.1%, 0.7%) of the maternal weight-adjusted dose (median (min, max) dose of 38 mg (30 mg, 120 mg), respectively). No adverse drug effects were reported for any of the infants.

8.4 Pediatric Use

The safety and effectiveness of REMERON/REMERONSolTab have not been established in pediatric patients with MDD. Two placebo-controlled trials in 258 pediatric patients with MDD have been conducted with REMERON, and the data were insufficient to establish the safety and effectiveness of REMERON/REMERONSolTab in pediatric patients with MDD.

Antidepressants increased the risk of suicidal thoughts and behaviors in pediatric patients [*see Boxed Warning and Warnings and Precautions (5.1)*].

In an 8-week-long clinical trial in pediatric patients receiving doses between 15 to 45 mg per day, 49% of REMERON-treated patients had a weight gain of at least 7%, compared to 5.7% of placebo-treated patients. The mean increase in weight was 4 kg (2 kg SD) for REMERON-treated patients versus 1 kg (2 kg SD) for placebo-treated patients [*see Warnings and Precautions (5.6)*].

8.5 Geriatric Use

Approximately 190 patients ≥65 years of age participated in clinical studies with REMERON. REMERON/REMERONSolTab 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. Pharmacokinetic studies revealed a decreased clearance of mirtazapine in the elderly [*see Clinical Pharmacology (12.3)*].

Sedating drugs, including REMERON/REMERONSolTab, may cause confusion and over-sedation in the elderly. Elderly patients may be at greater risk of developing hyponatremia. Caution is indicated when administering REMERON/REMERONSolTab to elderly patients [see *Warnings and Precautions (5.11), (5.14) and Clinical Pharmacology (12.3)*]. In general, dose selection for an elderly patient should be conservative, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

8.6 Renal or Hepatic Impairment

The clearance of mirtazapine is reduced in patients with moderate to severe renal or hepatic impairment. Consequently, plasma mirtazapine levels may be increased in these patient groups, compared to levels observed in patients without renal or hepatic impairment. Dosage decrease may be necessary when administering REMERON/REMERONSolTab to patients with moderate to severe renal or hepatic impairment [see *Warnings and Precautions (5.12), Use in Specific Populations (8.5), and Clinical Pharmacology (12.3)*].

8.7 Patients with Phenylketonuria

REMERONSolTab contains phenylalanine, a component of aspartame. REMERONSolTab contains the following amount of phenylalanine: 2.6 mg in 15 mg orally disintegrating tablet, 5.2 mg in 30 mg orally disintegrating tablet, and 7.8 mg in 45 mg orally disintegrating tablet [see *Warnings and Precautions (5.15)*].

10 OVERDOSAGE

Human Experience

In premarketing clinical studies, there were reports of REMERON overdose alone or in combination with other pharmacological agents. Signs and symptoms reported in association with overdose included disorientation, drowsiness, impaired memory, and tachycardia.

Based on postmarketing reports, serious outcomes (including fatalities) may occur at dosages higher than the recommended doses, especially with mixed overdoses. In these cases, QT prolongation and Torsades de Pointes have also been reported [see *Warnings and Precautions (5.5), Adverse Reactions (6.2), and Drug Interactions (7)*].

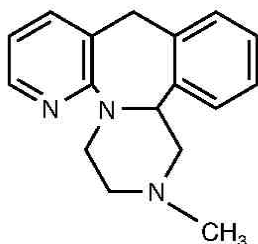
Overdose Management

No specific antidotes for mirtazapine are known.

Contact Poison Control (1-800-222-1222) for the latest recommendations.

11 DESCRIPTION

REMERON and REMERONSolTab contain mirtazapine. Mirtazapine has a tetracyclic chemical structure and belongs to the piperazino-azepine group of compounds. It is designated 1,2,3,4,10,14b-hexahydro-2-methylpyrazino [2,1-a] pyrido [2,3-c][2] benzazepine and has the empirical formula of C₁₇H₁₉N₃. Its molecular weight is 265.35. The structural formula is the following and it is the racemic mixture:



Mirtazapine is a white to creamy white crystalline powder which is practically insoluble in water.

REMERON is available for oral administration as scored film-coated tablets containing 15 or 30 mg of mirtazapine. Each tablet contains the following inactive ingredients: colloidal silicon dioxide anhydrous, corn starch, ferric oxide (yellow), hydroxypropyl cellulose, hypromellose, magnesium stearate, lactose monohydrate, polyethylene glycol 8000, and titanium dioxide. The 30 mg tablets also contain ferric oxide (red).

REMERONSolTab is available for oral administration as an orally disintegrating tablet containing 15, 30, or 45 mg of mirtazapine. REMERONSolTab also contains the following inactive ingredients: aspartame, citric acid anhydrous fine granular, crospovidone, hypromellose, magnesium stearate, mannitol, granular mannitol 2080, microcrystalline cellulose, natural and artificial orange flavor, polymethacrylate (Eudragit E100), povidone, sodium bicarbonate, and sugar spheres (composed of starch and sucrose).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The mechanism of action of mirtazapine for the treatment of major depressive disorder, is unclear. However, its efficacy could be mediated through its activity as an antagonist at central presynaptic α_2 -adrenergic inhibitory autoreceptors and heteroreceptors and enhancing central noradrenergic and serotonergic activity.

12.2 Pharmacodynamics

In preclinical studies, mirtazapine acts as an antagonist at α_2 -adrenergic inhibitory autoreceptors and heteroreceptors and as an antagonist at serotonin 5-HT₂ and 5-HT₃ receptors. Mirtazapine has no significant affinity for the 5-HT_{1A} and 5-HT_{1B} receptors.

Mirtazapine also acts as an antagonist of histamine (H₁) receptors, peripheral α_1 -adrenergic receptors, and muscarinic receptors. Actions at these receptors may explain some of the other clinical effects of mirtazapine (e.g., its prominent somnolent effects and orthostatic hypotension may be explained by its inhibition of histamine (H₁) receptors and peripheral α_1 -adrenergic receptors, respectively).

Cardiac Electrophysiology

The effect of REMERON (mirtazapine) on QTc interval was assessed in healthy subjects. At a dose of 75 mg (1.67 times the maximum recommended dosage), REMERON does not prolong the QTc interval to a clinically meaningful extent.

12.3 Pharmacokinetics

Plasma levels of mirtazapine are linearly related to dose over a dose range of 15 to 80 mg (1.78 times the maximum recommended dose). Steady state plasma levels of mirtazapine are attained within 5 days, with about 50% accumulation (accumulation ratio=1.5). The (–) enantiomer has an elimination half-life that is approximately twice as long as the (+) enantiomer and therefore achieves plasma levels that are about 3 times as high as that of the (+) enantiomer.

Absorption

Mirtazapine has an absolute bioavailability of about 50% following oral administration. Peak plasma concentrations of mirtazapine are reached within about 2 hours post dose.

Food Effect

The presence of food in the stomach has a minimal effect on both the rate and extent of absorption.

Distribution

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

Elimination

Mirtazapine has a half-life of about 20 to 40 hours following oral administration of REMERON or REMERONSoITab.

Metabolism

Mirtazapine is extensively metabolized after oral administration. Major pathways of bio-transformation are demethylation and hydroxylation followed by glucuronide conjugation. *In vitro* data from human liver microsomes indicate that CYP2D6 and CYP1A2 are involved in the formation of the 8-hydroxy metabolite of mirtazapine, whereas CYP3A is considered to be responsible for the formation of the N-desmethyl and N-oxide metabolite. Several unconjugated metabolites possess pharmacological activity but are present in the plasma at very low levels.

Excretion

Mirtazapine and its metabolites are eliminated predominantly (75%) via urine with 15% in feces.

Specific Populations

Geriatric Patients

Following oral administration of REMERON Tablets 20 mg/day for 7 days to subjects of varying ages (range 25 to 74 years old), oral clearance of mirtazapine was reduced in the elderly compared to the younger subjects. The clearance in elderly males was 40% lower compared to younger males, while the clearance was 10% lower in elderly females compared to younger females [see *Warnings and Precautions (5.14), Use in Specific Populations (8.5)*].

Male and Female Patients

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

Race

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

Patients with Renal Impairment

When compared to subjects with normal renal function, total body clearance of mirtazapine was reduced approximately 30% in renal impaired patients with GFR=11–39 mL/min/1.73 m² and approximately 50% in renal impaired patients with GFR=<10 mL/min/1.73 m²) [see *Warnings and Precautions (5.14), Use in Specific Populations (8.6)*].

Patients with Hepatic Impairment

Following a single 15-mg oral dose of REMERON, the oral clearance of mirtazapine in patients with hepatic impairment was decreased by approximately 30%, compared to subjects with normal hepatic function [see *Warnings and Precautions (5.12, 5.14), Use in Specific Populations (8.6)*].

Drug Interactions Studies

Warfarin

Mirtazapine (30 mg daily) at steady state caused a statistically significant increase (0.2) in the International Normalized Ratio (INR) in subjects treated with warfarin [see *Drug Interactions (7)*].

QTc-Prolonging Drugs

The risk of QT prolongation and/or ventricular arrhythmias (e.g., Torsades de Pointes) may be increased with concomitant use of medicines which prolong the QTc interval (e.g., some antipsychotics and antibiotics) and in mirtazapine overdose [see *Warnings and Precautions (5.5), Adverse Reactions (6.1, 6.2), Drug Interactions (7), and Overdosage (10)*].

Phenytoin

In healthy male subjects (n=18), phenytoin (200 mg daily, at steady state) increased mirtazapine (30 mg daily, at steady state) clearance about 2-fold, resulting in a decrease in average plasma mirtazapine

concentrations of 45% [see *Drug Interactions (7)*]. Mirtazapine did not significantly affect the pharmacokinetics of phenytoin.

Carbamazepine

In healthy male subjects (n=24), carbamazepine (400 mg twice a day, at steady state) increased mirtazapine (15 mg twice a day, at steady state) clearance about 2-fold, resulting in a decrease in average plasma mirtazapine concentrations of 60% [see *Drug Interactions (7)*].

Cimetidine

In healthy male subjects (n=12), when cimetidine, a weak inhibitor of CYP1A2, CYP2D6, and CYP3A4, given at 800 mg b.i.d. at steady state was coadministered with mirtazapine (30 mg daily) at steady state, the Area Under the Curve (AUC) of mirtazapine increased more than 50% [see *Drug Interactions (7)*]. Mirtazapine did not cause relevant changes in the pharmacokinetics of cimetidine.

Ketoconazole

In healthy male Caucasian subjects (n=24), coadministration of the strong CYP3A4 inhibitor ketoconazole (200 mg b.i.d. for 6.5 days) increased the peak plasma levels and the AUC of a single 30 mg dose of mirtazapine by approximately 40% and 50%, respectively [see *Drug Interactions (7)*].

Amitriptyline

In healthy, CYP2D6 extensive metabolizer patients (n=32), amitriptyline (75 mg daily), at steady state, did not cause relevant changes to the pharmacokinetics of steady state mirtazapine (30 mg daily); mirtazapine also did not cause relevant changes to the pharmacokinetics of amitriptyline.

Paroxetine

In healthy CYP2D6 extensive metabolizer subjects (n=24), mirtazapine (30 mg/day), at steady state, did not cause relevant changes in the pharmacokinetics of steady state paroxetine (40 mg/day), a CYP2D6 inhibitor.

Lithium

No relevant clinical effects or significant changes in pharmacokinetics have been observed in healthy male subjects on concurrent treatment with lithium 600 mg/day for 10 days at steady state and a single 30 mg dose of mirtazapine. The effects of higher doses of lithium on the pharmacokinetics of mirtazapine are unknown.

Risperidone

Mirtazapine (30 mg daily) at steady state did not influence the pharmacokinetics of risperidone (up to 3 mg twice a day) in subjects (n=6) in need of treatment with an antipsychotic and antidepressant drug.

Alcohol

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

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 has been shown to be additive with those caused by diazepam.

13 NONCLINICAL TOXICOLOGY

13.1 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, based on body surface

area (mg/m²) 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.

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), based on body surface area (mg/m²)]. 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.

14 CLINICAL STUDIES

The efficacy of REMERON as a treatment for major depressive disorder was established in 4 placebo-controlled, 6-week trials in adult outpatients meeting DSM-III criteria for major depressive disorder. Patients were titrated with REMERON from a dose range of 5 mg to 35 mg/day. The mean mirtazapine dose for patients who completed these 4 studies ranged from 21 to 32 mg/day. Overall, these studies demonstrated REMERON to be superior to placebo on at least 3 of the following 4 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 REMERON over placebo was also found for certain factors of the HDRS, including anxiety/somatization factor and sleep disturbance factor.

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

In a longer-term study, patients meeting (DSM-IV) criteria for major depressive disorder who had responded during an initial 8 to 12 weeks of acute treatment on REMERON were randomized to continuation of REMERON or placebo for up to 40 weeks of observation for relapse. Response during the open phase was defined as having achieved a HAM-D 17 total score of ≤8 and a CGI-Improvement score of 1 or 2 at 2 consecutive visits beginning with week 6 of the 8 to 12 weeks in the open-label phase of the study. Relapse during the double-blind phase was determined by the individual investigators. Patients receiving continued REMERON treatment experienced significantly lower relapse rates over the subsequent 40 weeks compared to those receiving placebo. This pattern was demonstrated in both male and female patients.

16 HOW SUPPLIED/STORAGE AND HANDLING

REMERON tablets are supplied as:

Tablet Strength	Tablet Color/Shape	Tablet Markings	Package Configuration	NDC Code
15 mg	Yellow, oval tablet	Scored with "MSD" debossed on one side and "T ₃ Z" on other side, on both sides of score line	Bottle / 30 count	78206-160-01
30 mg	Red-brown, oval tablet	Scored with "MSD" debossed on one side and "T ₅ Z" on other side, on both sides of score line	Bottle / 30 count	78206-161-01

Storage

Store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]. Protect from light and moisture.

REMERONSolTab orally disintegrating tablets are supplied as:

Tablet Strength	Tablet Color/Shape	Tablet Markings	Package Configuration	NDC Code
15 mg	White, round tablet	"T ₁ Z" debossed on one side.	Box of 5 x 6-unit dose blister packs/ 30 count	78206-156-01
30 mg	White, round tablet	"T ₂ Z" debossed on one side.	Box of 5 x 6-unit dose blister packs/30 count	78206-158-01
45 mg	White, round tablet	"T ₄ Z" debossed on one side	Box of 5 x 6-unit dose blister packs/30 count	78206-159-01

Storage

Store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]. Protect from light and moisture. Use immediately upon opening individual tablet blister.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Suicidal Thoughts and Behaviors

Advise patients and caregivers to look for the emergence of suicidality, especially early during treatment and when the dosage is adjusted up or down, and instruct them to report such symptoms to the healthcare provider [see *Boxed Warning and Warnings and Precautions (5.1)*].

Agranulocytosis

Advise patients to contact their physician if they experience fever, chills, sore throat, mucous membrane ulceration, flu-like complaints, or other symptoms that might suggest infection [see *Warnings and Precautions (5.2)*].

Serotonin Syndrome

Caution patients about the risk of serotonin syndrome, particularly with the concomitant use of REMERON/REMERONSolTab with other serotonergic drugs including triptans, tricyclic antidepressants, fentanyl, lithium, tramadol, tryptophan, buspirone, amphetamines, St. John's Wort, and with drugs that impair metabolism of serotonin (in particular, MAOIs, both those intended to treat psychiatric disorders and also others, such as linezolid). Advise patients to contact their healthcare provider or report to the emergency room if they experience signs or symptoms of serotonin syndrome [see *Dosage and Administration (2.4), Contraindications (4), Warnings and Precautions (5.3), Drug Interactions (7)*].

QT Prolongation and Torsades de Pointes

Inform patients to consult their physician immediately if they feel faint, lose consciousness, or have heart palpitations [see *Warnings and Precautions (5.5), Drug Interactions (7), Overdosage (10)*]. Advise patients to inform physicians that they are taking REMERON/REMERONSolTab before any new drug is taken.

Somnolence

Advise patients that REMERON/REMERONSolTab may impair judgment, thinking, and particularly, motor skills, because of its prominent sedative effect. Caution patients about performing activities requiring

mental alertness, such as operating hazardous machinery or operating a motor vehicle, until they are reasonably certain that REMERON/REMERONSoITab therapy does not adversely affect their ability to engage in such activities. [see *Warnings and Precautions (5.7)*].

Alcohol

Advise patients to avoid alcohol while taking REMERON/REMERONSoITab [see *Warnings and Precautions (5.7), Drug Interactions (7)*].

Activation of Mania/Hypomania

Advise patients and their caregivers to observe for signs of activation of mania/hypomania and instruct them to report such symptoms to the healthcare provider [see *Warnings and Precautions (5.8)*].

Discontinuation Syndrome

Advise patients not to abruptly discontinue REMERON/REMERONSoITab and to discuss any tapering regimen with their healthcare provider. Adverse reactions can occur when REMERON/REMERONSoITab is discontinued [see *Dosage and Administration (2.6), Warnings and Precautions (5.13)*].

Allergic Reactions

Advise patients to notify their healthcare provider if they develop an allergic reaction such as rash, hives, swelling, or difficulty breathing [see *Contraindications (4), Adverse Reactions (6.2)*].

Pregnancy

- Advise patients to notify their physician if they become pregnant or intend to become pregnant during REMERON/REMERONSoITab therapy.
- Advise patients that there is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to REMERON/REMERONSoITab during pregnancy [see *Use in Specific Populations (8.1)*].

Lactation

Advise patients to notify their physician if they are breastfeeding an infant [see *Use in Specific Populations (8.2)*].

Angle-Closure Glaucoma

Patients should be advised that taking REMERON can cause mild pupillary dilation, which in susceptible individuals, can lead to an episode of angle-closure glaucoma. Pre-existing glaucoma is almost always open-angle glaucoma because angle-closure glaucoma, when diagnosed, can be treated definitively with iridectomy. Open-angle glaucoma is not a risk factor for angle-closure glaucoma. Patients may wish to be examined to determine whether they are susceptible to angle-closure, and have a prophylactic procedure (e.g., iridectomy), if they are susceptible [see *Warnings and Precautions (5.4)*].

Patients with Phenylketonuria

Inform patients with phenylketonuria that REMERONSoITab contains phenylalanine [see *Warnings and Precautions (5.15)*].

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