PRODUCT MONOGRAPH

REMERON RD®

(mirtazapine)

Orally Disintegrating Tablets, 15, 30 and 45 mg

ANTI-DEPRESSANT

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Nonmedicinal Ingredients
oral	Orally Disintegrating Tablets, 15, 30 and 45 mg	Hydroxypropyl methylcellulose, povidone, sucrose, starch, polymethyl acrylate, magnesium stearate, mannitol, crospovidone, sodium bicarbonate, citric acid, microcrystalline cellulose, aspartame (contains phenylalanine), natural and artificial orange flavour are present as non-medicinal ingredients.

INDICATIONS AND CLINICAL USE

Adults
REMERON RD® (mirtazapine) is indicated for the symptomatic relief of depressive illness.

Long-term use of REMERON RD®
The efficacy of REMERON RD® Orally Disintegrating Tablets in maintaining a response in patients with major depressive disorder for up to 40 weeks following 8 - 12 weeks of initial open-label treatment was demonstrated in a placebo-controlled trial. Nevertheless, the physician who elects to use REMERON RD® for extended periods should periodically evaluate the long-term response of the individual patient to the drug.

Geriatrics (> 65 years of age):
Evidence from clinical trials and experience suggests that use in geriatric populations may be associated with differences in safety or effectiveness. A brief discussion can be found in the appropriate sections [see WARNINGS AND PRECAUTIONS, Neurologic, Somnolence; Special Populations, Geriatrics (> 65 years of age); DOSAGE AND ADMINISTRATION; ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions, Geriatrics].

Pediatrics (< 18 years of age):
REMERON RD® is not indicated for use in patients below the age of 18 years (see WARNINGS AND PRECAUTIONS, General, Potential Association with Behavioural and Emotional Changes, Including Self-Harm; see also ADVERSE REACTIONS/Pediatrics, DOSAGE AND ADMINISTRATION and ACTION AND CLINICAL PHARMACOLOGY Special Populations and Conditions/Pediatrics).

CONTRAINDICATIONS

Hypersensitivity: REMERON RD® is contraindicated in patients who are known to be hypersensitive to the drug or any of its components. For a complete listing, see DOSAGE FORMS, COMPOSITION AND PACKAGING.

Monoamine Oxidase Inhibitors:
In patients receiving agents that may affect the serotonergic neurotransmitter systems in combination with a monoamine oxidase (MAO) inhibitor, there have been reports of serious, sometimes fatal, reactions including hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delirium and coma. These reactions have also been reported in patients who have recently discontinued (SSRI) Selective Serotonin Reuptake Inhibitor treatment and have begun treatment on a MAO inhibitor. Some cases presented with features resembling serotonin syndrome or neuroleptic malignant syndrome (see WARNINGS AND PRECAUTIONS, Neurologic, Serotonin Syndrome/Neuroleptic Malignant Syndrome).

Therefore, REMERON RD® should not be used in combination with MAO inhibitors (including the antibiotic linezolid, and the thiazine dye methylthioninium blue (methylene blue), which are less well-known examples of MAO inhibitors) or within a minimum of 2 weeks of terminating treatment with MAO inhibitors. Treatment with REMERON RD® should then be initiated cautiously and dosage increased gradually until optimal response is reached. MAO inhibitors should not be introduced within 2 weeks of cessation of therapy with REMERON RD®.

WARNINGS AND PRECAUTIONS

General

POTENTIAL ASSOCIATION WITH BEHAVIOURAL AND EMOTIONAL CHANGES, INCLUDING SELF-HARM

Pediatrics: Placebo-Controlled Clinical Trial Data

- **Recent analyses of placebo-controlled clinical trial safety databases from SSRIs (Selective Serotonin Reuptake Inhibitors) and other newer anti-depressants suggest that use of these drugs in patients under the age of 18 may be associated with behavioural and emotional changes, including an increased risk of suicidal ideation and behaviour over that of placebo.**
- **The small denominators in the clinical trial database, as well as the variability in placebo rates, preclude reliable conclusions on the relative safety profiles among these drugs.**

Adults and Pediatrics: Additional Data

There are clinical trial and post-marketing reports with SSRIs and other newer anti-depressants, in both pediatrics and adults, of severe agitation-type adverse events coupled with self-harm or harm to others. The agitation-type events include: akathisia, agitation, disinhibition, emotional lability, hostility, aggression, and depersonalization. In some cases, the events occurred within several weeks of starting treatment.

Rigorous clinical monitoring for suicidal ideation or other indicators of potential for suicidal behaviour is advised in patients of all ages. This includes monitoring for agitation-type emotional and behavioural changes.

Discontinuation Symptoms
Patients currently taking REMERON RD® should NOT discontinue treatment abruptly, due to risk of discontinuation symptoms. At the time that a medical decision is made to discontinue an SSRI or other newer anti-depressant drug, a gradual reduction in the dose, rather than an abrupt cessation, is recommended.

Sucrose
REMERON RD® contains sucrose, therefore, patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

Aspartame
REMERON RD® contains aspartame, a source of phenylalanine, therefore, may be harmful for people with phenylketonuria.

Agranulocytosis
In pre-marketing clinical trials, two (one with Sjögren's Syndrome) out of 2,796 patients treated with REMERON® Tablets and one patient treated with imipramine developed agranulocytosis. In all three cases, the patients recovered after the drug with which they were being treated was stopped. In the post-marketing period with REMERON®, very rare cases of agranulocytosis have been reported, mostly reversible, but in some cases fatal. Fatal cases have mostly concerned patients above 65 years of age, although there has been at least one such fatality in a younger patient. Patients who are to receive REMERON RD® should be warned about the risk of developing agranulocytosis, and advised to contact their physician if they experience any indication of infection such as fever, chills, sore throat, mucous membrane ulceration. If a patient develops a sore throat, fever, stomatitis or other signs of infection, along with a low WBC count, treatment with REMERON RD® Orally Disintegrating Tablets should be discontinued and the patient should be closely monitored.

Discontinuation of Treatment with REMERON RD®
When discontinuing treatment, patients should be monitored for symptoms which may be associated with discontinuation, e.g., 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 (see ADVERSE REACTIONS). A gradual reduction in the dosage over several weeks, rather than abrupt cessation, is recommended whenever possible. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, dose titration should be managed on the basis of the patient's clinical response (see ADVERSE REACTIONS and DOSAGE AND ADMINISTRATION)**.**

The following additional precautions are listed alphabetically.

Carcinogenesis and Mutagenesis
See TOXICOLOGY for animal data.

Cardiovascular

QT Prolongation / Torsade de Pointes: Cases of QT prolongation, torsades de pointes (TdeP), ventricular tachycardia, ventricular fibrillation, cardiac arrest, and sudden death, have been

reported during the post-marketing use of REMERON®. 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, Drug-Drug Interactions and OVERDOSAGE). Caution should be exercised when REMERON® is prescribed in patients with known cardiovascular disease or family history of QT prolongation, and in concomitant use with other medicinal products thought to prolong the QTc interval. Torsade de pointes may be asymptomatic or experienced by the patient as dizziness, palpitations, syncope, or seizures. If sustained, torsade de pointes can progress to ventricular fibrillation and sudden cardiac death.

The effect of REMERON® (mirtazapine) on QTc interval was assessed in a randomised, placebo and positive controlled (moxifloxacin 400 and 800 mg) clinical trial using exposure response analysis in 54 healthy volunteers. This study revealed that both 45 mg (therapeutic) and 75 mg (supratherapeutic) doses of mirtazapine, unlike moxiflozacin, did not affect the QTc interval to a clinically significant meaningful extent.

However, because TdeP, including ventricular fibrillation and sudden death have been reported during postmarketing use of REMERON®, it should be taken into consideration that, under certain situations, these events may occur during treatment with mirtazapine.

Cholesterol/Triglycerides: In U.S. short-term controlled studies, non-fasting cholesterol increases of > 20% above the upper limits of normal were observed in 15% of patients taking REMERON® Tablets compared to 7% for placebo. In these same studies, non-fasting triglycerides increased to > 500 mg/dl in 6% of patients taking REMERON® Tablets compared to 3 % for placebo.

Concomitant Illness

Use in Patients with Concomitant Illness: Clinical experience with mirtazapine in patients with concomitant systemic illness is limited. Accordingly, care is advisable in prescribing REMERON RD® for patients with diseases or conditions that affect metabolism or hemodynamic responses.

Cardiovascular-Related History

Mirtazapine has not been systematically evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or other significant heart disease. Mirtazapine was associated with significant orthostatic hypotension in early clinical pharmacology trials with normal human volunteers. Orthostatic hypotension was infrequently observed in clinical trials with depressed patients. REMERON RD® 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).

Dependence/Tolerance

Physical and Psychological Dependence: Mirtazapine has not been systematically studied in animals or humans for its potential for abuse, tolerance or physical dependence. While the clinical trials did not reveal any tendency for any drug-seeking behaviour, 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 RD® misuse or abuse (e.g., development of

tolerance, incrementation of dose, drug-seeking behaviour).

Endocrine and Metabolism

Increased Appetite/Weight Gain: In U.S. short-term controlled studies the use of REMERON® Tablets was associated with increased appetite in 17% and the complaint of weight gain in 12% of patients, compared to 2% for placebo in both cases. In these same trials, weight gain of ≥ 7% occurred in 7.5% of the patients taking REMERON® Tablets compared to 0% in patients taking placebo. The average weight gain in the U.S. long-term controlled trials was 8 lbs. over 28 weeks.

Diabetes: Care should be taken in patients with diabetes mellitus. In patients with diabetes, antidepressants may alter glycaemia control. Insulin and/or oral hypoglycaemic dosage may need to be adjusted and close monitoring is recommended.

Hyponatremia: Hyponatremia has been reported very rarely with the use of mirtazapine. Caution should be exercised in patients at risk, such as elderly patients or patients concomitantly treated with medications known to cause hyponatremia.

Genitourinary

Although mirtazapine has very weak anticholinergic activity, care should be taken in patients with micturition disturbances like prostate hypertrophy.

Hematologic

Please refer to WARNINGS AND PRECAUTIONS, General, Agranulocytosis.

Hepatic/Biliary/Pancreatic

Hepatic Impairment: Increased plasma concentrations of mirtazapine occur in patients with moderate and severe hepatic impairment (see ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions). In such patients, upward dose titration should be carefully monitored (see DOSAGE AND ADMINISTRATION).

Transaminase Elevations: In U.S. short-term controlled studies, clinically significant ALT (SGPT) elevations (3 times the normal range) were noted in 2%, respectively, of patients treated with REMERON® Tablets and in 0% of patients treated with placebo. Most patients did not develop signs or symptoms associated with compromised liver function. While some patients discontinued treatment due to ALT increases, other patients with elevations continued with enzyme levels returning to normal during ongoing treatment. Mirtazapine should be used with caution in patients with impaired hepatic function (see DOSAGE AND ADMINISTRATION).

Jaundice: Treatment should be discontinued if jaundice occurs.

Neurologic

Somnolence: The use of REMERON® Tablets was associated with somnolence in 54% of patients in U.S. short-term controlled studies, compared to 18% with placebo. In these studies, somnolence resulted in of 10% of mirtazapine-treated patients discontinuing treatment compared to 2% of placebo-treated patients. REMERON RD® Orally Disintegrating Tablets may cause mental or motor impairment because of this prominent sedative effect. Thus, patients should be cautioned about engaging in hazardous activities, such as driving a car or operating dangerous machines, until they are reasonably certain that REMERON RD® therapy does not adversely affect their ability to engage in such activities.

Akathisia/Psychomotor Restlessness
The use of antidepressants have been associated with the development of akathisia, characterized by a subjectively unpleasant or distressing restlessness and need to move, often accompanied by an inability to sit or stand still. This is most likely to occur within the first few weeks of treatment. In patients who develop these symptoms, increasing the dose may be detrimental.

Dizziness: In U.S. short-term controlled studies, the use of REMERON® Tablets was associated with dizziness in 7% of patients, compared to 3% for placebo.

Activation of Mania/Hypomania: Mania/hypomania occurred in approximately 0.2% (3/1,299 patients) of REMERON®-treated patients in all U.S. studies (controlled and non-controlled). Although the incidence of mania/hypomania was very low during treatment with REMERON® Tablets, it should be used carefully in patients with a history of mania/hypomania.

Seizures: In pre-marketing clinical trials, only one seizure was reported in the 2,796 U.S. and non-U.S. patients treated with REMERON® Tablets. However, no controlled studies have been carried out in patients with a history of seizures. Therefore care should be exercised when REMERON RD® is used in these patients.

Serotonin Syndrome/Neuroleptic Malignant Syndrome: On rare occasions serotonin syndrome or neuroleptic malignant syndrome-like events have occurred in association with treatment of REMERON RD®, particularly when given in combination with other serotonergic and/or neuroleptic/antipsychotic drugs. As these syndromes may result in potentially life-threatening conditions, treatment with REMERON RD® should be discontinued if patients develop a combination of symptoms possibly including hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, mental status changes including confusion, irritability, extreme agitation progressing to delirium and coma and supportive symptomatic treatment should be initiated. Due to the risk of serotonergic syndrome or neuroleptic malignant syndrome REMERON RD® should not be used in combination with MAO inhibitors (including the antibiotic linezolid and the thiazine dye methylthioninium chloride (methylene blue) which are less well-known examples of MAOIs) or serotonin-precursors (such as L-tryptophan, oxitriptan) and should be used with caution in patients receiving other serotonergic drugs (triptans, lithium, tramadol, St. John's Wort, most tricyclic antidepressants) or neuroleptics/antipsychotics (see CONTRAINDICATIONS and DRUG INTERACTIONS).

<u>Ophthalmologic</u>
Care should be taken in patients with acute narrow-angle glaucoma and increased intra-ocular pressure.

<u>Psychiatric</u>
Suicide: Depression is associated with an increased risk of suicidal thoughts, self harm and suicide (suicide-related events). This risk persists until significant remission occurs. As with any patient receiving anti-depressants, high-risk patients should be closely supervised during initial drug therapy. As improvement may not occur during the first few weeks or more of treatment, patients should be closely monitored until such improvement occurs. It is general clinical experience that the risk of suicide may increase in the early stages of recovery. Patients with a history of suicide-related events or those exhibiting a significant degree of suicidal ideation prior

to commencement of treatment are known to be at greater risk of suicidal thoughts or suicide attempts, and should receive careful monitoring during treatment.

In addition, a FDA meta-analysis of placebo-controlled clinical trials of antidepressants in adult patients with psychiatric disorders showed an increased risk of suicidal behavior with antidepressants compared to placebo in patients less than 25 years old.

Prescriptions of REMERON RD® should be written for the smallest amount consistent with good patient management, in order to reduce the risk of overdose (see WARNINGS AND PRECAUTIONS, General, Potential Association with Behavioural and Emotional Changes, Including Self-Harm).

Renal

Renal and Hepatic Impairment: Increased plasma concentrations of mirtazapine occur in patients with moderate and severe renal impairment and, to a lesser extent, in patients with hepatic impairment (see ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions). In such patients, upward dose titration should be carefully monitored (see DOSAGE AND ADMINISTRATION).

Special Populations

Pregnant Women: Safe use of REMERON RD® during pregnancy has not been established. Therefore, it should not be administered to women of childbearing potential or nursing mothers unless, in the opinion of the treating physician, the expected benefits to the patient outweigh the possible hazards to the child or fetus.

Complications following late third trimester exposure to newer antidepressants:
Post-marketing reports indicate that some neonates exposed to SSRIs (Selective Serotonin Reuptake Inhibitors) or other newer anti-depressants, such as REMERON RD®, late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support and tube feeding. Such complications can arise immediately upon delivery. Reported clinical findings have included respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability and constant crying. The frequency of symptoms may vary with each drug. These features are consistent with either a direct toxic effect of SSRIs and other newer anti-depressants, or, possibly, a drug discontinuation syndrome. It should be noted that, in some cases, the clinical picture is consistent with serotonin syndrome (see WARNINGS AND PRECAUTIONS, Neurologic, Serotonin Syndrome/Neuroleptic Malignant Syndrome). When treating a pregnant woman with REMERON RD® during the third trimester, the physician should carefully consider the potential risks and benefits of treatment (see DOSAGE AND ADMINISTRATION).

The extent of exposure in pregnancy during clinical trials: None.

Nursing Women: Safe use of REMERON RD® during lactation has not been established. Animal data and limited human data have detected mirtazapine in breast milk in low concentrations. A decision whether to continue/discontinue therapy with REMERON RD®, or to continue/discontinue breast feeding should be made, taking into account the benefits and possible hazards to mother and infant.

Pediatrics (< 18 years of age): Safety and efficacy in children under 18 years of age have not

been established. REMERON RD® is not indicated for use in patients below the age of 18 years (see WARNINGS AND PRECAUTIONS, General, Potential Association with Behavioural and Emotional Changes, Including Self-Harm; see also ADVERSE REACTIONS, Pediatrics; DOSAGE AND ADMINISTRATION and ACTION AND CLINICAL PHARMACOLOGY Special Populations and Conditions/Pediatrics).

Long-term safety data in children and adolescents concerning growth, maturation and cognitive and behavioral development are lacking.

Geriatrics (> 65 years of age): Pharmacokinetic studies revealed a decreased clearance in the elderly, with the lowest clearance in elderly females. Elderly patients may be more susceptible to adverse events such as sedation, dizziness or confusion. Care should be exercised in dosage and titration to higher doses (see ACTION AND CLINICAL PHARMACOLOGY; DOSAGE AND ADMINISTRATION and WARNINGS AND PRECAUTIONS, Neurologic, Somnolence).

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Adverse Events Leading to Discontinuation of Treatment:
Sixteen percent of patients treated with REMERON® Tablets in U.S. short-term controlled studies discontinued treatment due to an adverse event, compared to 7% of patients treated with placebo. The adverse event that accounted for more than 5% of discontinuations with REMERON® Tablets was somnolence (10%).

Commonly Observed Adverse Events in U.S. Short-Term Controlled Clinical Trials: The most commonly observed adverse events related to the use of REMERON® Tablets (5% or greater drug-related incidence for REMERON® Tablets and at least twice that of placebo) were: somnolence (54% vs. 18%), increased appetite (17% vs. 2%), weight gain (12% vs. 2%), dizziness (7% vs. 3%).

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse drug reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

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 among REMERON®-treated patients (and greater than the incidence in placebo-treated patients) who participated in U.S. short-term placebo-controlled trials, in which patients were dosed in a range of 5 to 60 mg/day. The investigators reported adverse clinical experiences using terms of their own choice. Reported adverse events were then classified using the 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.

Table 1: Incidence of adverse clinical experiences (≥ 1% for REMERON® Tablets) in U.S. short-term placebo-controlled studies[1,2,3]

Body System Adverse Event	REMERON® Tablets N = 453	Placebo N = 361
Body as a Whole		
Asthenia	34 (8%)	17 (5%)
Flu Syndrome	22 (5%)	9 (3%)
Back Pain	9 (2%)	3 (1%)
Digestive System		
Dry Mouth	112 (25%)	54 (15%)
Increased Appetite	76 (17%)	7 (2%)
Constipation	57 (13%)	24 (7%)
Metabolic and Nutritional Disorders		
Weight Gain	54 (12%)	6 (2%)
Peripheral Edema	11 (2%)	4 (1%)
Edema	6 (1%)	1 (0%)
Musculoskeletal System		
Myalgia	9 (2%)	3 (1%)
Nervous System		
Somnolence	243 (54%)	65 (18%)
Dizziness	33 (7%)	12 (3%)
Abnormal Dreams	19 (4%)	5 (1%)
Thinking Abnormal	15 (3%)	4 (1%)
Tremor	7 (2%)	2 (1%)
Confusion	9 (2%)	1 (0%)
Respiratory System		
Dyspnea	5 (1%)	1 (0%)
Urogenital System		
Urinary Frequency	8 (2%)	5 (1%)

N = Number of Patients

1 % rounded off to the nearest whole integer.

2 Events which had an incidence on placebo > Remeron® Tablets: infection, pain, headache, nausea, diarrhea and insomnia.

3 Events which had an incidence of Remeron® Tablets comparable to placebo: chest pain, palpitation, tachycardia, postural hypotension, dyspepsia, flatulence, libido decreased, hypertonia, nervousness, rhinitis, pharyngitis, sweating, amblyopia, tinnitus and taste perversion.

There was evidence of adaptation to some adverse events with continued therapy (e.g., increased appetite, dizziness and somnolence).

ECG Changes: The electrocardiograms for 338 patients who received REMERON® Tablets and 261 patients who received placebo in the U.S. short-term controlled trials were analyzed, in which the QTc calculations using the method of Fridericia was employed. 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.

Less Common Clinical Trial Adverse Drug Reactions (< 1%)

During worldwide controlled and uncontrolled clinical trials, REMERON® Tablets were administered to 2,796 patients. The listing of events which follows includes those events which were judged by the investigator to be adverse clinical experiences. The investigators used terminology of their own choice to describe the adverse experiences. 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 categories. It is important to emphasize that although the events occurred during treatment with REMERON® Tablets, they were not necessarily drug-related. Following the adverse experience tabulations, the incidence of clinically significant laboratory values which occurred at a rate of ≥ 1% of patients is presented.

In the tabulations that follow, adverse events as reported by the investigator were classified using a standard COSTART-based Dictionary terminology. 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 1/1,000 patients; **rare** events are those occurring in fewer than 1/1,000 patients. Only those events not already listed in Table 1 appear in this listing. Events of major clinical importance are also described in the WARNINGS AND PRECAUTIONS section.

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, substernal chest pain.

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 discolouration, 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 Systems: 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, arthosis, bursitis.

Nervous System: frequent: hypoesthesia, apathy, depression, hypokinesia, vertigo, twitching, agitation, anxiety, amnesia, hyperkinesia, paresthesia; **infrequent:** aggression, ataxia, delirium, delusions, depersonalization, dyskinesia, extrapyramidial 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.

Pediatrics

The following adverse events were observed commonly in clinical trials in children: significant weight gain (≥7 %) was observed in 48.8 % of the REMERON® treated subjects compared to 5.7 % in the placebo arm; urticaria (11.8 % vs. 6.8 %) and hypertriglyceridaemia (2.9 % vs. 0 %) were also commonly observed. (See also ACTION AND CLINICAL PHARMACOLOGY Special Populations and Conditions/Pediatrics).

Abnormal Hematologic and Clinical Chemistry Findings

Abnormal Laboratory Values: Elevated cholesterol, serum glucose and triglycerides were the most common blood chemistry parameters observed in U.S. studies.

The plasma samples were drawn from non-fasting patients, and these parameters are affected by diet. Patients taking REMERON® Tablets had increased appetite and weight gain, and are likely to have had increased food intake. Increased food intake may account for the increased triglyceride and cholesterol values. Moreover, LDL:HDL ratio data from a limited number of patients suggest that fat metabolism does not change with REMERON® treatment, further suggesting that the increase in triglyceride and cholesterol values reflected increased dietary intake.

Mild changes in liver function are shown by increases in liver enzymes. However, changes are temporary, mild, and are not expected to negatively influence liver function. Premature terminations due to liver enzyme abnormalities were, respectively, REMERON® Tablets, 1.7% and placebo, 1.1%.

The incidence of neutropenias in all clinical studies for REMERON® Tablets was 1.5%. Most of the observed cases of neutropenia were mild, isolated and nonprogressive (see WARNINGS AND PRECAUTIONS).

Post-Market Adverse Drug Reactions

Adverse Events Observed During Post-Marketing Evaluation of REMERON® Tablets

Adverse events reported after market introduction, which were temporally (but not necessarily causally) related to mirtazapine therapy and which were not reported in clinical trials.

Adverse events are listed under the appropriate System Organ Class

Blood and lymphatic system disorders: bone marrow depression (granulocytopenia, agranulocytopenia, aplastic anemia) (see also WARNINGS AND PRECAUTIONS, Agranulocytosis), eosinophilia.

Metabolism and nutrition disorders: hyponatremia.

Psychiatric disorders: insomnia, nightmares, psychomotor restlessness, suicidal ideation, suicidal behaviours.

Nervous system disorders: headache, oral paresthesia, serotonin syndrome, restless legs, syncope, lethargy, sedation.

Investigations: electrocardiogram QT prolonged, increased creatine kinase.

Cardiac disorders: cardiac arrest, long QT, torsade de pointes (see WARNINGS AND PRECAUTIONS, QT Prolongation / Torsade de Pointes), sudden death, ventricular arrhythmia (torsade de pointes), ventricular fibrillation, ventricular tachycardia.

Vascular disorders: orthostatic hypotension

Gastrointestinal disorders: diarrhea, mouth edema, oral hypoaesthesia.

Skin and subcutaneous tissue disorders: Stevens-Johnson syndrome, dermatitis bullous, erythema multiforme, toxic epidermal necrolysis.

Musculoskeletal and connective tissue disorders: rhabdomyolysis.

General disorders and administration site conditions: Generalized and local edema, fatigue.

Adverse Reactions Following Discontinuation of Treatment (or Dose Reduction)

There have been reports of adverse reactions upon the discontinuation of REMERON® Tablets (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 (see WARNINGS AND PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Patients should be monitored for these or any other symptoms. A gradual reduction in the dosage over several weeks, rather than abrupt cessation, is recommended whenever possible. If intolerable symptoms occur following a decrease in dose or upon discontinuation of treatment, dose titration should be managed on the basis of the patient's clinical response. These events are generally self-limiting. Symptoms associated with discontinuation have been reported for other anti-depressants with serotonergic effects (see WARNINGS AND PRECAUTIONS and DOSAGE AND ADMINISTRATION).

DRUG INTERACTIONS

Serious Drug Interactions

- **Monoamine Oxidase Inhibitors: See CONTRAINDICATIONS**

Overview

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 ACTION AND CLINICAL PHARMACOLOGY).

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

Mirtazapine is extensively metabolized by CYP2D6, CYP3A4, and to a lesser extent by CYP1A2.

Drug-Drug Interactions

Monoamine Oxidase Inhibitors: Combined use of REMERON RD® and monoamine oxidase inhibitors **(including the antibiotic linezolid and the thiazine dye methylthioninium chloride (methylene blue) which are less well-known examples of MAOIs)** is contraindicated due to the potential for serious reactions with features resembling serotonin syndrome or neuroleptic malignant syndrome (see CONTRAINDICATIONS and WARNINGS AND PRECAUTIONS, Neurologic, Serotonin Syndrome/Neuroleptic Malignant Syndrome).

Drugs Known to Prolong the QT Interval: 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 case of mirtazapine overdose.

Diazepam: The impairment of motor skills produced by mirtazapine has been shown to be additive with those caused by diazepam. Accordingly, patients should be advised to avoid diazepam and other similar drugs while taking REMERON RD®.

CYP Enzyme Inducers

CYP3A4 Inducers (these studies used both drugs at steady state):

- **Phenytoin:** In healthy male patients (n=18), phenytoin (200 mg daily) increased mirtazapine (30 mg daily) clearance, resulting in about a twofold decrease in plasma mirtazapine concentrations. Mirtazapine did not significantly affect the pharmacokinetics of phenytoin. During combined use of mirtazapine and phenytoin, 3 out of 19 patients

experienced fatigue and 1 out of 19 patients developed rash (and none had experienced either fatigue or rash with mirtazapine alone or phenytoin alone). The rash was severe enough to necessitate withdrawal from the study.

- **Carbamazepine:** In healthy male patients (n=24), carbamazepine (400 mg b.i.d.) increased mirtazapine (15 mg b.i.d.) clearance, resulting in about a twofold decrease in plasma mirtazapine concentrations.

When phenytoin, carbamazepine or another inducer of hepatic metabolism (such as rifampicin) is added to mirtazapine therapy, the mirtazapine dose may have to be increased. If treatment with such a medicinal product is discontinued, it may be necessary to reduce the mirtazapine dose.

CYP Enzyme Inhibitors

Cimetidine: In healthy male patients (n=12), when cimetidine (800 mg b.i.d.) at steady state was co-administered with mirtazapine (30 mg daily) at steady state, the Area Under the Curve (AUC) of mirtazapine increased by about 60%. Mirtazapine did not significantly change the pharmacokinetics of cimetidine. During combined use, side effects included somnolence [10 of 12 patients (including 1 of moderate severity) vs. 7 of 12 with mirtazapine alone and none with cimetidine alone], arrhythmia (2 of 12 patients vs. none with mirtazapine or cimetidine alone). The mirtazapine dose may have to be decreased when concomitant treatment with cimetidine is started, or increased when cimetidine treatment is discontinued.

Ketoconazole: In healthy, male, Caucasian patients (n=24), co-administration of the potent 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 mirtazapine by approximately 40% and 50% respectively. During combined use, 2 severe adverse events have been reported: One patient experienced circulatory collapse and another patient experienced syncope. Both patients have lost consciousness for a brief period. Caution should be exercised when co-administering mirtazapine with potent CYP3A4 inhibitors, HIV protease inhibitors, azole antifungals, erythromycin or nefazodone.

Paroxetine: In an *in vivo* interaction study in healthy, CYP2D6 extensive metabolizer patients (n=24), mirtazapine (30 mg/day), at steady state, did not significantly change the pharmacokinetics of steady state paroxetine (40 mg/day), a CYP2D6 inhibitor. However, plasma concentrations of mirtazapine and its demethyl metabolite were slightly higher (about 18 and 25%, respectively) during combined administration with paroxetine. This difference is considered to be without clinical relevance. During combined use, side effects included exanthema (1 of 24 patients) that required withdrawal of the patient. Increases in AST and ALT were also reported, with a greater increase in men due to several outliers (including a patient that was withdrawn due to high AST (about 4 fold higher than the upper normal limit) and ALT (about 2 fold higher than the upper normal limit) levels; this patient also showed elevated WBC, neutrophils, decreased lymphocytes and basophils). AST/ALT levels returned to normal following the end of the treatment. Caution is advised for the co-administration of paroxetine with mirtazapine.

Other Drug-Drug Interactions

Amitriptyline: In healthy, CYP2D6 extensive metabolizer patients (n=32), amitriptyline (75 mg daily), at steady state, did not change the pharmacokinetics of steady state mirtazapine (30 mg daily) considerably and mirtazapine also did not change the pharmacokinetics of amitriptyline considerably. During combined use the following adverse reactions have been reported at considerably higher frequencies than with either drug alone: postural hypotension, impaired

concentration (about 5 fold higher incidence), nausea (over 4 fold higher incidence) and dizziness (about 2 fold higher incidence). A CYP2D6 slow metabolizer patient experienced a serious adverse event following combined use of amitriptyline and mirtazapine. The subject complained of abdominal discomfort accompanied by dizziness and nausea and then leading to loss of consciousness for about 30 s. Apart from slight tremor (resembling myoclonic contractions) there were no other abnormalities. Caution is advised for the co-administration of amitriptyline with mirtazapine.

Warfarin: In healthy male subjects (n=16) mirtazapine (30 mg daily), at steady state, caused a small (0.2) but statistically significant increase in the International Normalised Ratio (INR) in subjects treated with warfarin to achieve subtherapeutic levels of prothrombin activity (1.5-2.0 INR) at steady state. As at a higher dose of mirtazapine, a more pronounced effect can not be excluded, it is advisable to monitor the INR in case of concomitant treatment of warfarin with mirtazapine.

Lithium: No relevant clinical effects or significant changes in pharmacokinetics have been observed in healthy male subjects on concurrent treatment with subtherapeutic levels of lithium (600 mg/day for 10 days) at steady state and a single 30 mg dose of mirtazapine. The serum levels of lithium were approximately 0.3 mmol/L 10 hrs after dosing. The effects of higher doses of lithium on the pharmacokinetics of mirtazapine are unknown.

Risperidone: In an *in vivo* non-randomized, interaction study subjects (n=6) in need of treatment with an antipsychotic and antidepressant drug, the results of the effect of mirtazapine (30 mg daily) at steady state on the pharmacokinetics of risperidone (up to 3 mg b.i.d.) at steady state is inconclusive, due to high inter-patient variability and low number of patients. The study design does not permit conclusions to be made on the safety on the combined use of mirtazapine and risperidone. However, a case report of a male patient receiving combined treatment with mirtazapine (60 mg daily) and risperidone (3 mg daily) documents that, 6 weeks after initiation of this combination therapy, the patient developed pulmonary embolism and rhabdomyolysis. Caution is advised for the co-administration of risperidone with mirtazapine.

Serotonergic Drugs:
Based on the mechanism of action of mirtazapine and the potential for serotonin syndrome, caution is advised when REMERON RD® is co-administered with other drugs or agents that may affect the serotonergic neurotransmitter systems, such as tryptophan, triptans, serotonin reuptake inhibitors, lithium, tramadol, linezolid, methylene blue or St. John's Wort (see CONTRAINDICATIONS and WARNINGS AND PRECAUTIONS, Serotonin Syndrome/Neuroleptic Malignant Syndrome).

Drugs Bound to Plasma Protein: Because mirtazapine is bound to plasma proteins (85%), care should be exercised when REMERON RD® is co-administered to a patient who may be receiving another drug which is highly protein-bound.

Drug-Herb Interactions
St. John's Wort: Pharmacodynamic interactions between REMERON RD® and the herbal remedy St. John's Wort may occur and may result in an increase in undesirable effects. Dose adjustment of REMERON RD® should be considered if clinically indicated.

Drug-Lifestyle Interactions

Alcohol: The impairment of mental and motor skills produced by mirtazapine has been shown to be additive with those produced by alcohol. Accordingly, patients should be advised to avoid alcohol while taking REMERON RD®.

DOSAGE AND ADMINISTRATION

REMERON RD® is not indicated for use in children under 18 years of age (see WARNINGS AND PRECAUTIONS, POTENTIAL ASSOCIATION WITH BEHAVIOURAL AND EMOTIONAL CHANGES, INCLUDING SELF-HARM).

REMERON RD® Orally Disintegrating Tablets are unique tablets that are designed to rapidly disintegrate on the tongue. No water is needed to take the tablets.

Dosing Considerations

TREATMENT OF PREGNANT WOMEN DURING THE THIRD TRIMESTER:

Post-marketing reports indicate that some neonates exposed to SSRI's or other newer anti-depressants, such as REMERON RD®, late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support and tube feeding (see WARNINGS AND PRECAUTIONS). When treating pregnant women with REMERON RD® during the third trimester, the physician should carefully consider the potential risks and benefits of treatment. The physician may consider tapering REMERON RD® in the third trimester.

Children:

See WARNINGS AND PRECAUTIONS, POTENTIAL ASSOCIATION WITH BEHAVIOURAL AND EMOTIONAL CHANGES, INCLUDING SELF-HARM.

ELDERLY AND PATIENTS WITH MODERATE TO SEVERE RENAL OR HEPATIC IMPAIRMENT: In elderly patients, and patients with moderate to severe renal or hepatic impairment, limited pharmacokinetic data (see ACTION AND CLINICAL PHARMACOLOGY) demonstrates increased serum concentration and/or reduced clearance of REMERON® Tablets. REMERON RD® should thus be dosed with care in these populations (see ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics).

Recommended Dose and Dosage Adjustment

INITIAL TREATMENT

ADULTS:

REMERON RD® Orally Disintegrating Tablets should be administered as a single dose, preferably in the evening prior to sleep. The recommended initial dose is 15 mg daily. In clinical trials, patients generally received doses of REMERON® Tablets in the range of 15 - 45 mg/day. While a relationship between dose and anti-depressant response for mirtazapine has not been established, patients not responding to the initial 15 mg dose may benefit from dose increases up to a maximum of 45 mg/day (see ACTION AND CLINICAL PHARMACOLOGY, Clinical Trials Showing Efficacy). Mirtazapine has an elimination half-life of approximately 20 - 40 hours, therefore, dose changes should occur in intervals of not less than one week. Dosage adjustments may be made according to the tolerance and based on the patient's response.

LONGER-TERM TREATMENT

It is generally agreed that acute episodes of depression require several months or longer of sustained therapy beyond response to the acute episode. Systematic evaluation of REMERON® has demonstrated that its efficacy in major depressive disorder is maintained for periods of up to 40 weeks following 8 - 12 weeks of initial treatment at a dose of 15 - 45 mg/day (see ACTION AND CLINICAL PHARMACOLOGY). Based on these limited data, it is unknown whether or not the dose of REMERON RD® needed for continuation treatment is identical to the dose needed to achieve an initial response. Patients should be periodically reassessed to determine the need for continuation treatment and the appropriate dose for such treatment.

DISCONTINUATION OF REMERON RD® TREATMENT

Symptoms associated with the discontinuation or dose reduction of REMERON RD® Tablets have been reported. Patients should be monitored for these and other symptoms when discontinuing treatment or during dosage reduction of REMERON RD® (see WARNINGS AND PRECAUTIONS and ADVERSE REACTIONS).

A gradual reduction in the dose over several weeks, rather than abrupt cessation, is recommended whenever is possible. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, dose titration should be managed on the basis of the patient's clinical response (see WARNINGS AND PRECAUTIONS and ADVERSE REACTIONS).

Missed Dose

Do not take a double dose to make up for forgotten doses.

If a patient forgets to take the evening dose, advise the patient not to take the missed dose the next morning. Continue treatment in the evening (prior to sleep) with the normal dose.

Administration

Administration of REMERON RD® 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 the blister; once removed, it cannot be stored. REMERON RD® 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 tablets (see PART III - **CONSUMER INFORMATION**).

OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

Human Experience: In clinical trials, the only drug overdose death reported while taking REMERON® (mirtazapine) Tablets was in combination with amitriptyline and chlorprohixene 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 chlorprohixene were found to be at toxic levels. In other pre-marketing overdose cases with REMERON® Tablets, the following signs and symptoms were reported: disorientation, drowsiness, impaired memory and tachycardia. There were no

reports of ECG abnormalities, coma or convulsions following overdose with REMERON® Tablets alone.

In post-marketing experience with more than 35 million patients exposed to REMERON® (based on average treatment courses of 30 mg/day during 3 months), fatal cases of overdose with REMERON® alone have been reported. In many cases details regarding the precise dose are lacking. Fatal acute overdoses with REMERON® alone are documented at doses as low as approximately 440 mg, which is estimated from the post-mortem plasma levels, assuming linear pharmacokinetics. However, survival has also been reported with a single REMERON® overdose as high as 1,350 mg.

Present experience concerning overdose with REMERON® alone indicates that symptoms are usually mild. Depression of the central nervous system with disorientation and prolonged sedation have been reported, together with tachycardia and mild hyper- or hypotension. However, there is a possibility of more serious outcomes (including fatalities) at dosages much higher than the therapeutic dose, especially with mixed overdosages. In these cases QT prolongation and Torsade de Pointes have also been reported.

Overdose Management: Treatment should consist of those general measures employed in the management of overdose with any anti-depressant.

Ensure an adequate airway, oxygenation and ventilation. Monitor vital signs and cardiac rhythm (ECG monitoring should be undertaken). General supportive and symptomatic measures are also recommended. Induction of emesis is not recommended. Activated charcoal or gastric lavage may be appropriate.

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 centre for additional information on the treatment of any overdose.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

The mechanism of action of REMERON RD® Tablets, as with other drugs effective in the treatment of major depressive disorder, is unknown.

Evidence gathered in preclinical studies suggests that mirtazapine enhances central noradrenergic and serotonergic activity. These studies have shown that mirtazapine acts as an antagonist at central presynaptic α2-adrenergic inhibitory autoreceptors and heteroreceptors, an action that is postulated to result in an increase in central noradrenergic and serotonergic activity. The clinical relevance of this finding is unknown.

Pharmacodynamics

Mirtazapine acts as an antagonist at central presynaptic α_2 adrenergic inhibitory autoreceptors and heteroreceptors, which results in an increase in central noradrenergic and serotonergic

activity. The clinical relevance of this finding is unknown, however, this action may explain its anti-depressant activity.

Mirtazapine is a potent antagonist of 5-HT_2 and 5-HT_3 receptors. The clinical relevance of this finding is unclear, however, the 5-HT_2 and 5-HT_3 antagonism by mirtazapine may account for its low rate of nausea, insomnia and anxiety as observed in clinical trials. Mirtazapine has no significant effect on 5-HT_{1A} and 5-HT_{1B} receptors.

Both enantiomers of mirtazapine appear to contribute to its pharmacological activity. The (+)enantiomer blocks 5-HT_2 receptors as well as α_2 receptors, and the (-)enantiomer blocks 5-HT_3 receptors. The clinical relevance of this finding is unclear, but this may explain its anti-depressant activity and side-effect profile.

Mirtazapine is a potent histamine (H_1) receptor antagonist, which may contribute to its sedative effect and possibly to weight gain due to increased appetite.

Mirtazapine is a moderate peripheral α_1 adrenergic antagonist, a property which 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 occasional occurrence of anticholinergic side effects associated with its use as shown in clinical trials.

Pharmacokinetics

Mirtazapine is well absorbed following oral administration and its absolute bioavailability is approximately 50% after either single or multiple doses. Peak plasma concentrations are reached within about 2 hours following an oral dose. The time to peak plasma concentration is independent of dose. The presence of food in the stomach somewhat slows the rate but not the extent of absorption, and thus does not require a dosage adjustment.

Plasma levels are linear over a dose range of 30 to 80 mg. Steady-state plasma levels are attained within about 5 days. The half-life of elimination of mirtazapine after oral administration is approximately 20 - 40 hours.

REMERON RD® Orally Disintegrating Tablets have been found to be bioequivalent to REMERON® Tablets.

Metabolism: Mirtazapine is extensively metabolized and quantitatively eliminated via urine (75%) and feces (15%); approximately 90% of this elimination occurs within the first 72 - 96 hours. Major pathways of biotransformation are demethylation and oxidation followed by 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-demethyl and N-oxide metabolite. The demethyl metabolite is pharmacologically active and appears to have a similar pharmacokinetic profile as that of the parent compound.

The (-)enantiomer has an elimination half-life that is approximately twice as long, and achieves plasma levels that are three times as high as that of the (+)enantiomer.

Protein Binding: Mirtazapine is approximately 85% bound to plasma proteins over a concentration range of 10 to 1,000 ng/mL. Binding appears to be both non-specific and reversible. The binding affinity of mirtazapine to human liver proteins is 2.8 times greater than to human plasma proteins. As with all drugs that are protein-bound, care should be exercised when co-administering medications that may interact with mirtazapine at protein-binding sites (see WARNINGS AND PRECAUTIONS).

Table 2: Effect of age and gender on plasma half-life of mirtazapine

	$T_{½}$ (MEAN ± SD)*	
Group	**Single Dose**	**Multiple Dose**
Adult male N=9	21.7 ± 4.2	22.1 ± 3.7
Adult female N=9	37.7 ± 13.3	35.4 ± 13.7
Elderly# male N=8	32.2 ± 15.4	31.1 ± 15.1
Elderly# female N=8	40.6 ± 12.8	39.0 ± 10.8

* Expressed in hours.

The "elderly" group consisted of subjects 55 and older (55 - 75; mean age 65)

Special Populations and Conditions

Pediatrics: REMERON RD® is not indicated for use in patients below the age of 18 years. Two randomised, double-blind, placebo-controlled trials in children aged between 7 and 18 years with major depressive disorder (n=259) failed to demonstrate significant differences between mirtazapine and placebo on the primary and all secondary endpoints. Significant weight gain (≥7 %) was observed in 48.8 % of the REMERON® treated subjects compared to 5.7 % in the placebo arm. Urticaria (11.8 % vs. 6.8 %) and hypertriglyceridaemia (2.9 % vs. 0 %) were also commonly observed. (see WARNINGS AND PRECAUTIONS, General, **Potential Association with Behavioural and Emotional Changes, Including Self-Harm**; and **DOSAGE AND ADMINISTRATION**).

Geriatrics: Following administration of mirtazapine 20 mg/day for 7 days, oral clearance was reduced in older subjects (mean age 65; range 55 - 75) compared to younger subjects (see Table 2). The difference was greatest in males, with a 40% lower clearance for mirtazapine in the older vs. younger group, while clearance is lowest overall in elderly females. Caution is indicated in administering REMERON RD® Orally Disintegrating Tablets in the elderly (see WARNINGS AND PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Gender:

Age and Sex: In the same study above (see ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions, Geriatrics) females of all ages (range 25 - 74) exhibited significantly longer elimination half-lives than males (mean half-life of 37 hours for females vs. 26 hours for males) (see Table 2). Although these differences result on average in higher AUC for females compared to males, there is considerable overlap in individual AUCs between groups. Because of substantial individual variation of AUC and half-life, no specific dosage recommendations based on sex are indicated (see DOSAGE AND ADMINISTRATION).

Hepatic Insufficiency:

Liver Disease: In a single-dose study conducted with mirtazapine 15 mg, the elimination half-

life of mirtazapine was increased 40% in mild to moderately hepatically impaired subjects as compared to patients with normal hepatic function; this effect on elimination resulted in a 57% increase in AUC and a 33% decrease in clearance.

Renal Insufficiency:
Renal Disease: In a single-dose study conducted with mirtazapine 15 mg, subjects with moderate and severe renal impairment showed a significant decrease in the clearance of mirtazapine and a consequent increase in AUC (54% and 215% for moderate and severe renal impairment, respectively). Subjects with severe renal impairment had significantly higher peak plasma levels of mirtazapine (about double that of subjects without renal impairment). These results suggest that caution must be exercised in administering REMERON RD® to patients who may have compromised renal function.

STORAGE AND STABILITY

Store at controlled room temperature, 15°C - 30°C. Protect from light and moisture. Use immediately upon opening individual tablet blister.

SPECIAL HANDLING INSTRUCTIONS

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 the blister; once removed, it cannot be stored. REMERON RD® 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 tablets.

DOSAGE FORMS, COMPOSITION AND PACKAGING

REMERON RD® Orally Disintegrating Tablets are supplied as:

15 mg Tablets – white, flat-faced, round, bevelled edge tablets, coded with TZ1, with a characteristic orange odour; available in boxes of 30 (5 x 6 unit Dose Blisters).

30 mg Tablets – white, flat-faced, round, bevelled edge tablets, coded with TZ2, with a characteristic orange odour; available in boxes of 30 (5 x 6 unit Dose Blisters).

45 mg Tablets – white, flat-faced, round, bevelled edge tablets, coded with TZ4, with a characteristic orange odour; available in boxes of 30 (5 x 6 unit Dose Blisters).

Composition: Each tablet contains 15 mg, 30 mg or 45 mg of mirtazapine. Hydroxypropyl methylcellulose, povidone, sucrose, starch, polymethyl acrylate, magnesium stearate, mannitol, crospovidone, sodium bicarbonate, citric acid, microcrystalline cellulose, aspartame (contains phenylalanine), natural and artificial orange flavour are present as non-medicinal ingredients.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

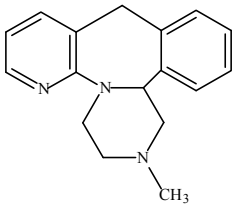
Drug Substance

Proper name: Mirtazapine

Chemical name: 1,2,3,4,10,14b-hexahydro-2-methylpyrazino [2,1-a] pyrido [2,3-c] benzazepine

Molecular formula and molecular mass: $C_{17}H_{19}N_3$ and 265.36

Structural formula:



Physicochemical properties:

pKa: (Water, 25°C) 7.7

pH: [0.1% solution in water/dioxane (9/1)] 8.85

Partition coefficient: [octonal/water], 25°C Log P = 3.3

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

CLINICAL TRIALS

Clinical Trials Showing Efficacy

The efficacy of REMERON® Tablets in the treatment of depression was demonstrated in four U.S. placebo-controlled trials (6 week duration) in adult outpatients meeting DSM III criteria for major depression. Patients were titrated with mirtazapine starting at a dose of 5 mg/day up to a dose of 35 mg/day (by the beginning of Week 3). Outcome measures included the Hamilton Depression Rating Scale (21-item) and the Montgomery and Asberg Depression Rating Scale. The mean mirtazapine dose for patients completing the four studies ranged from 21 to 32 mg/day. Additional supportive studies used higher doses up to 50 mg/day.

In the U.S. short-term flexible-dose controlled trials (REMERON® Tablets, n=323), 70% and 54% of the patients received final doses ≥ 20 mg and ≥ 25 mg, respectively.

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® Tablets were randomized to continuation of REMERON® Tablets or placebo for up to 40 weeks of observation for relapse. Response during the open phase was defined as having achieved a HAMD-17 total score of ≤ 8 and a CGI-Improvement score of 1 or 2 at two consecutive visits, beginning with Week 6 of the 8 - 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.

Comparative Bioavailability Studies
REMERON RD® Orally Disintegrating Tablets have been found to be bioequivalent to REMERON® Tablets (open, cross-over study; n=40, under fasting conditions).

Table 3: Summary table of the comparative bioavailability data
REMERON RD® orally disintegrating tablets
(1 x 30 mg)
From measured data
Geometric Mean
Arithmetic Mean (CV%)

PARAMETER	TEST	REFERENCE*	% RATIO OF GEOMETRIC MEANS	90% CONFIDENCE INTERVAL
$AUC_{0-tlast}$ (ng.hr/mL)	646 677 (29.3)	620 652 (30.0)	104	100-109
$AUC_{0-\infty}$ (ng.hr/mL)	691 728 (31.0)	668 705 (31.8)	104	100-108
C_{max} (ng/mL)	71.1 76.3 (37.3)	75.9 80.6 (34.4)	94	84-105
T_{max}** (h)	1.50 (0.75-4.00)	1.00 (0.75-3.00)		
$T_{1/2}$ *** (h)	27.1 (27.7)	27.8 (26.5)		

* Reference - REMERON® Tablets, Schering-Plough Canada Inc. (purchased in Canada)
** Median (minimum - maximum) is presented
*** Arithmetic mean (CV %)

DETAILED PHARMACOLOGY

Mirtazapine and its enantiomers have been studied for their pharmacological effects in behavioural models for depression (Table 4) in mice and rats and in EEG-derived rat sleep-waking analysis and in receptor interaction studies [receptors for noradrenaline, serotonin (5-HT), histamine, acetylcholine and dopamine in rats and guinea pigs].

Table 4: CNS-Pharmacological profile of mirtazapine and its enantiomers

CNS-Pharmacological Profile	Mirtazapine	(S)+enant.	(R)-enant.
Behavioural models			
Anti-depressant-like effects			
- bulbectomized rat: behavioural	+	+	-
biochemical	+	-	+
- acquired immobility test	-	-	+
Anti-anxiety effects			
- anxiosoif test	±	±	±
EEG studies			
Anti-depressant profile			
- sleep (rat)	+	+	±
- sleep (human)	+	+	+
Receptor interactions			
Noradrenaline (α_2-blockade)			
- enhancement NA release	+	+	-
- rauwolscine displacement	+	+	-
- antagonism clonidine mydriasis	+	+	-
Serotonin			
- affinity $5HT_2$	+	+	±
- affinity $5HT_3$	+	-	+
Histamine			
- H_1-antagonism	+	+	+
Acetylcholine			
- QNB binding	-	-	-
- guinea pig ileum	-	-	-

Pharmacological Indices of Side-Effects (Table 4)
The commonly observed side-effects of anti-depressants that can be ascribed to receptor interactions are those of anticholinergic (dry mouth, blurred vision, constipation, urinary retention), α_1-adrenolytic (orthostatic hypotension) and antihistaminic (sedation) origin.

Mirtazapine is virtually devoid of anticholinergic activity, as has been shown in *in vitro* receptor interactions and confirmed in the *in vivo* tremorine antagonism test. It is therefore predicted that the incidence of anticholinergic side-effects observed with mirtazapine in clinical practice should be low. This has been confirmed in clinical trials.

Mirtazapine is a moderately weak antagonist at central and peripheral α_1-adrenoceptors, as observed *in vitro* in the labelled prazosin binding assay in rat brain cortex homogenates and in the isolated rat vas deferens assay. On the basis of these observations, a low incidence of orthostatic hypotension would be predicted, which is in line with the clinical observations in depressed patients.

Contribution of Mirtazapine Enantiomers to its Pharmacological Profile (Table 4)
In the acquired immobility test for anti-depressant activity, both mirtazapine and the (S)+enantiomer are inactive, whereas the (R)-enantiomer is active.

In the olfactory bulbectomized rat, subchronic treatment with the (S)+enantiomer reverses deficient behaviour, whereas the (R)-enantiomer is inactive. However, the bulbectomy-induced decreases in noradrenaline and MHPG levels are reversed by subchronic treatment with the (R)-enantiomer, but not with the (S)+enantiomer.

Both enantiomers are active in the conflict-punishment test (display anti-anxiety activity) and in the sleep-waking EEG test in rats (suppression of REM sleep, an effect shared by many psychotropic drugs). In human pharmaco-EEG profiling in healthy volunteers (16), both enantiomers show a clear-cut "anti-depressant" profile at similar dose levels (0.5 and 1 mg per subject).

The enantiomers of mirtazapine differ considerably with respect to biochemical activity. The α_2-blocking activity of mirtazapine is virtually confined to the (S)+enantiomer, which is also the more potent $5HT_2$ antagonist. However, the (R)-enantiomer is the active principle in mirtazapine with regard to $5HT_3$ antagonistic activity. Both enantiomers contribute to a similar extent to the antihistaminic and (weak) α_1-adrenolytic properties of mirtazapine.

Contribution of Mirtazapine Main Metabolites to its Pharmacological Profile
Demethyl mirtazapine, the only metabolite found in the rat brain after oral administration of REMERON®, has anti-anxiety activity in the conflict-punishment test in rats, but is less active in the rat EEG profile for anti-depressant activity than the parent compound. The demethyl metabolite is also less active than the parent compound in *in vivo* tests for α_2-blocking and $5HT_2$ antagonistic activity. This may be due to poor bioavailability upon systemic administration, since the *in vitro* tests show that the compound is approximately equally active to mirtazapine as an α_2 and $5HT_2$ antagonist, important indices for therapeutic anti-depressant activity. With respect to antagonism at the histamine H_1 receptor, which is probably related to sedation, the demethyl metabolite appears to be less active than the parent compound.

8-hydroxy mirtazapine, 8-hydroxy demethyl mirtazapine and N(2)-oxide of mirtazapine have not been found to penetrate into the rat brain and are inactive *in vivo*, with the exception of the N(2)-oxide and the 8-hydroxy metabolite, which display some anti-serotonergic activity. *In vitro*, these metabolites are much less active than the parent compound at important receptors, like the α_2, $5HT_2$ and histamine H_1 receptors. They are, therefore, not considered to be relevant for the pharmacodynamic profile of mirtazapine, with regard to therapeutic activity or side- effects.

Glucuronide and sulphonate conjugates are not expected to be pharmacologically active and therefore only a limited number of *in vivo* and *in vitro* tests have been performed with these metabolites; they did not show any activity.

Cardiovascular Pharmacology of Mirtazapine
Cardiovascular effects
In conscious rabbits, mirtazapine, at doses of 0.1 and 1.0 mg/kg i.v., has no effect on blood pressure, heart rate and the autonomic nervous system; at 10 mg/kg i.v., mirtazapine also has no effect on blood pressure and heart rate, but slightly reduces the noradrenaline-induced increase in blood pressure and isoprenaline-induced increase in heart rate.

In anesthetized cats, mirtazapine, at doses of 0.1 and 1.0 mg/kg i.v., induces no cardiovascular effects and does not affect the autonomic nervous system; at 10 mg/kg i.v., mirtazapine induces a decrease in blood pressure and heart rate and reduces the changes in blood pressure induced by vagus stimulation and carotid occlusion.

Hemodynamic effects
In anesthetized dogs, mirtazapine, at 0.1 mg/kg i.v., does not induce any hemodynamic changes; at 1.0 mg/kg i.v., mirtazapine slightly decreases heart rate and myocardial contractility and

slightly increases peripheral vascular resistance; at 10 mg/kg i.v., mirtazapine induces a slight decrease in heart rate and stroke index, resulting in a slightly decreased cardiac index, a decrease in myocardial contractility and an increase in peripheral vascular resistance, resulting in decreased femoral and common carotid blood flow.

Cardiotoxicity

In artificially ventilated, anesthetized dogs, cardiotoxicity has been investigated by infusing mirtazapine intravenously (30 mg/kg/h) until the animal died from cardiac arrest. If the animal was still alive 5 hours after the start of the infusion, the experiment was stopped. Four out of five dogs died at the end of the 5-hour infusion period and one dog survived the infusion period. The mean extrapolated plasma level of mirtazapine prior to death in these four dogs was approximately 20 μg/mL; this is approximately 200 times the anticipated clinical peak plasma levels. There was a linear relationship between the severity of the cardiovascular effects (e.g., decrease in blood pressure, decrease in cardiac output and decrease in dP/dt) and the measured plasma level of mirtazapine.

TOXICOLOGY

Acute toxicity

The oral LD_{50} value for mirtazapine in male Swiss mice was 830 mg/kg (760 - 940 mg/kg) after 24 hours and 810 mg/kg (720 - 1,010 mg/kg) after 7 days, and in females, 720 mg/kg (620 - 850 mg/kg) after 24 hours and 7 days.

The oral LD_{50} value for mirtazapine after 24 hours and 7 days was 490 mg/kg (427 - 534 mg/kg) and 320 mg/kg (240 - 430 mg/kg) in male and female Wistar rats, respectively. In a separate study in rats, the enantiomers of mirtazapine displayed similar acute toxicity, the LD_{50} being 222 mg/kg and 208 mg/kg for the (R)- and (S)+enantiomers, respectively.

Clinical signs observed in both species, mainly at the highest doses, included motor incoordination, reduced activity, ptosis, twitches, abnormally slow respiration and piloerection; these symptoms reached their peak 2 hours after administration and gradually disappeared during the first day. Gross anatomy revealed no drug-related morphological changes.

Repeated dose toxicity

Oral 13-week toxicity studies were carried out with mirtazapine in rats of both sexes followed by a 4-week recovery period with daily doses of 10, 40 and 120 mg/kg, and in dogs of both sexes followed by a 7-week recovery period at daily doses of 5, 20 and 80 mg/kg. A second study in dogs was performed at a single dose level of 20 mg/kg/day to investigate possible changes in the prostate seen in the initial study in male dogs. One-year toxicity studies, followed by a five-week recovery period, were carried out in rats and dogs with daily doses of 2.5, 20 and 120 mg/kg and 2.5, 15 and 80 mg/kg, respectively.

Subchronic toxicity

Oral administration of mirtazapine at 10 mg/kg/day to Wistar rats for 13 consecutive weeks induced no untoward effects, whereas mirtazapine at 40 and 120 mg/kg/day induced:

- transient clinical signs including mydriasis, lachrymation, ptosis, hypothermia, bradypnoea and hypersalivation (only females receiving 120 mg/kg)
- transient decrease in body weight gain and initial decrease in food consumption followed by an increase in food intake

- increased thyroidal weight (males only) associated with hypertrophy of thyroid follicular cells, a finding known to occur with compounds inducing microsomal hepatic enzymes in this species (see rat carcinogenicity study)
- increased adrenal gland weight (females only) not associated with morphological changes
- mild vacuolation of cortical renal tubules not associated with any other cytoplasmic or nuclear changes suggestive of degenerative/necrotic response, lipid deposition or any disturbances in renal function tests; this is not a nephrotoxic response as confirmed in the subsequent chronic toxicity study (see below)
- mild hepatic cell hypertrophy not indicative of hepatotoxicity and not accompanied by hepatic functional disturbances or degenerative changes

All these findings were reversible after a 4-week post-dosing period.

Oral administration of mirtazapine to Beagle dogs for 13 consecutive weeks induced:
- increased liver weights not associated with hepatotoxicity at dose levels of 5, 20 and 80 mg/kg/day
- behavioural changes including incidental vomiting, loose defecation, reduced motor activity and body tremors at 20 and 80 mg/kg/day
- slight body weight loss in male dogs at 80 mg/kg/day
- decreased red blood cell parameters (hemoglobin and packed cell volume) at 80 mg/kg/day
- decreased testicular weight associated with reduced spermatogenesis, decreased epididymal weights and reduced epididymal spermatozoal content in two out of five animals at 80 mg/kg/day

A significant decrease in prostatic weights was seen in all drug-treated animals, as well as in a male in the control group kept for recovery. This effect was evaluated in a supplementary study (20 mg/kg/day for 13 consecutive weeks), after which it was concluded that the prostatic weight changes found in the first study most probably were not due to mirtazapine treatment but related to seasonal variations and age differences (younger males appearing to be more sensitive to changes in prostatic weight than the older animals). There is no evidence from the clinical studies to suggest that mirtazapine will affect the prostate in man.

Chronic toxicity
Oral administration of mirtazapine for one year to Sprague-Dawley rats (2.5, 20 and 120 mg/kg/day) and Beagle dogs (2.5, 15 and 80 mg/kg/day) did not induce any effects additional to those observed in the subchronic toxicity studies.

In the rat study, body weight in low-dose (males and females) and mid-dose (females) groups was generally slightly lower than in control animals; there was a marked decrease in body weight in the high-dose animals.

Microscopic examinations revealed that the only drug-related finding was an increased incidence of intracytoplasmic vacuolation in the renal proximal convoluted tubules in the high-dose group of rats after 6 months, and those of the high- and intermediate-dose groups after 12 months. In addition, there was an increased incidence of finely granular brown pigment in the cytoplasm of the tubular epithelial cells in the high-dose rats. The above-mentioned changes were not accompanied by any cytoplasmic or nuclear degenerative changes or by any disturbance in the renal function tests. From the light microscopy it was suggested that the vacuolations are the result of an increase in the size and numbers of the vacuoles constituting the

endocytotic/lysosomal system in the proximal convoluted tubules. This was verified by electron microscopic examination of the kidneys. Vacuolations are known to occur whenever there is an incompatibility between material that enters the lysosomes and the digestive enzymes stored there. Thus, in the chronic toxicity study with mirtazapine in rats, a transient incompatibility may have taken place due to overloading with the high dose of the test material. As in the subchronic thirteen-week study, tubular vacuolation and brown pigmentation were reversed during the one-month recovery period.

Oral administration of mirtazapine at 2.5 and 15 mg/kg/day to Beagle dogs for 12 months induced no untoward effects, whereas at 80 mg/kg/day, induced:

- neurological signs (trembling and convulsions)
- decline in condition and mild gastro-intestinal disturbances
- body weight loss mainly during the first half of the dosing period
- decreases in red blood cell parameters (RBC, Hb, PCV)
- mild increases in alkaline phosphatase and glutamic-pyruvic transaminase during the first half of the dosing period, together with liver enlargement and hepatic cell hypertrophy, possibly indicative of enzyme induction. These changes were not associated with hepatic morphological changes indicative of hepatotoxicity after six or twelve months
- increases in the erythroid/myeloid ratios in the bone marrow in males and, to a lesser extent, females receiving 15 or 80 mg/kg/day after 52 weeks of dosing due to mildly decreased total myeloid elements in males and females and mildly increased erythroid elements in males

Reversibility of the drug-related effects was seen after the one-month post-dosing period.

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. Based on AUC exposure, the highest doses used were approximately 0.7 and 1.2 times the maximum recommended human dose (MRHD) of 45 mg/day 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 tumours 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 enough to fully characterize the carcinogenic potential of REMERON RD® Orally Disintegrating 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 (1.9 times the MRHD on an AUC basis*).* Mating and conception were not affected by the drug, but estrous cycling was disrupted at doses that were 1.3 times MRHD based on AUC*,* and pre-implantation losses occurred at 1.9 times MRHD based on AUC.

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PART III: CONSUMER INFORMATION

REMERON RD®
(mirtazapine)

This leaflet is part III of a three-part "Product Monograph" published when REMERON RD® was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about REMERON RD®. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
REMERON RD® belongs to a group of medicines known as anti-depressants.

REMERON RD® has been prescribed to you to relieve your symptoms of depression. **Treatment with these types of medications is most safe and effective when you and your doctor have good communication about how you are feeling.**

What it does:
The way REMERON RD® works to treat depression is unknown. REMERON RD® is thought to have an effect in the brain on chemicals called serotonin and norepinephrine.

When it should not be used:
Do not use REMERON RD® if you are:
- allergic to it or any of the components (see section What the important non-medicinal ingredients are);
- currently taking or have recently taken monoamine oxidase (MAO) inhibitors (including some types of anti-depressants and anti-Parkinson treatments) (see section INTERACTIONS WITH THIS MEDICATION).

What the medicinal ingredient is:
Mirtazapine

What the important nonmedicinal ingredients are:
Aspartame (contains phenylalanine), citric acid, crospovidone, hydroxypropyl methylcellulose, magnesium stearate, mannitol, microcrystalline cellulose, natural and artificial orange flavour, polymethyl acrylate, povidone, sodium bicarbonate, starch and sucrose.

What dosage forms it comes in:
Orally disintegrating tablet as a white, flat-faced, round, bevelled edge tablet with a characteristic orange odour, coded with TZ1, TZ2, and TZ4 for the 15 mg, 30 mg, and 45 mg tablets, respectively.

WARNINGS AND PRECAUTIONS

During treatment with these types of medications, it is important that you and your doctor have good ongoing communication about how you are feeling.

REMERON RD® is not for use in children under 18 years of age.

Changes in Feelings and Behaviour:
It is important that you have good communication with your doctor about how you feel. Discussing your feelings and treatment with a friend or relative who can tell you if they think you are getting worse is also useful.

Some patients may feel worse when first starting or changing the dose of drugs such as REMERON RD®. You may feel more anxious or may have thoughts of hurting yourself or others, especially if you have had thoughts of hurting yourself before. These changes in feelings can happen in patients treated with drugs like REMERON RD® for any condition, and at any age, although it may be more likely if you are aged 18 to 24 years old. **If this happens, see your doctor immediately.** Do not stop taking REMERON RD® on your own.

BEFORE you use REMERON RD®, talk to your doctor or pharmacist:
- if you have ever had an allergic reaction to any medication;
- if you have QT/QTc prolongation or a family history of QT/QTc prolongation;
- if you have heart disease;
- about all your medical conditions, including a history of seizures, liver or kidney disease, heart problems, such as certain kinds of heart conditions that may change your heart rhythm, a recent heart attack, heart failure, or take certain medicines that may affect the heart's rhythm, diabetes, low blood pressure, glaucoma (increased intra-ocular pressure), high cholesterol and/or high triglycerides (fats in the blood), difficulties in urinating as a result of an enlarged prostate, psychiatric diseases such as schizophrenia and bipolar disorder (alternating periods of elation/overactivity and depressed mood);
- about any medications (prescription or non-prescription) which you are taking (refer to the next section for specific interactions with REMERON RD®);
- about any natural or herbal products you are taking (e.g., St. John's Wort);
- if you are pregnant or thinking of becoming pregnant, or if you are breastfeeding;
- about your habits of alcohol consumption;
- if you have been told by your doctor that you have an intolerance to some sugars.

REMERON RD® contains a source of phenylalanine. It may be harmful for people with phenylketonuria.

REMERON RD® is not for use in children under 18 years of age.

Refrain from potentially hazardous tasks, such as driving a car or operating dangerous machines, until you are certain that this medication does not affect your mental alertness or physical coordination.

Contact your physician before stopping or reducing your dosage of REMERON RD®. Symptoms such as dizziness, abnormal dreams, electric shock sensations, agitation, anxiety, difficulty concentrating, headache, tremor, nausea, vomiting, sweating or other symptoms may occur after stopping or reducing the dosage of REMERON RD®. Such symptoms may also occur if a dose is missed. These symptoms usually disappear without needing treatment. Tell your doctor immediately if you have these or any

other symptoms. Your doctor may adjust the dosage of REMERON RD® to alleviate the symptoms.

Effects on Pregnancy and Newborns

If you are already taking/using REMERON and have just found out that you are pregnant, you should talk to your doctor immediately. You should also talk to your doctor if you are planning to become pregnant.

Possible complications at birth (from taking any newer antidepressant, including REMERON):

Post-marketing reports indicate that some newborns whose mothers took an SSRI (Selective Serotonin Reuptake Inhibitor) or other newer anti-depressants, such as REMERON RD®, during pregnancy have developed complications at birth requiring prolonged hospitalization, breathing support and tube feeding. Reported symptoms include: feeding and/or breathing difficulties, seizures, tense or overly relaxed muscles, jitteriness and constant crying. In most cases, the newer anti-depressant was taken during the third trimester of pregnancy. These symptoms are consistent with either a direct adverse effect of the anti-depressant on the baby, or possibly a discontinuation syndrome caused by sudden withdrawal from the drug. These symptoms normally resolve over time. However, if your baby experiences any of these symptoms, contact your doctor as soon as you can.

If you are pregnant, or nursing, and taking an SSRI or other newer anti-depressants, such as REMERON RD®, you should discuss the risks and benefits of the various treatment options with your doctor. It is very important that you do NOT stop taking these medications without first consulting your doctor. See also SIDE EFFECTS AND WHAT TO DO ABOUT THEM section.

INTERACTIONS WITH THIS MEDICATION

Serious Drug Interactions

Do not use REMERON if you are taking or have recently taken:

- Monoamine oxidase inhibitor (e.g., phenelzine, tranylcypromine, moclobemide, selegiline, linezolid, methylene blue)
- Thioridazine
- Pimozide

You should tell your doctor if you are taking or have recently taken any medications (prescription, non-prescription or natural/herbal), especially:

- other antidepressants, such as SSRIs, venlafaxine and certain tricyclics
- other drugs that affect serotonin such as tryptophan, triptans, lithium, tramadol, methylene blue (used to treat high levels of methemoglobin in the blood), St. John's Wort
- ketoconazole(medicine for treating fungal infections)
- cimetidine (used to treat reflux and stomach ulcers)
- erythromycin [used to treat bacterial infections (antibiotic)]
- drugs used to treat Human Immunodeficiency Virus (HIV), such as a combination of fosamprenavir and ritonavir
- nefazodone (used to treat depression)
- certain drugs used to treat epilepsy, such as carbamazepine and phenytoin
- rifampicin (used to treat tuberculosis)
- warfarin (used to prevent blood clotting)
- benzodiazepines (e.g., midazolam, oxazepam and diazepam) – as REMERON RD® may add to the sedative effects of these agents.
- medicines that may affect the heart's rhythm such as certain antibiotics and some anti-psychotics.

Avoid alcoholic drinks while taking REMERON RD®.

PROPER USE OF THIS MEDICATION

Usual dose:

It is very important that you take REMERON RD® exactly as your doctor has instructed. Generally, most people take between 15 mg and 45 mg per day.

How to take REMERON RD®:

- Never increase or decrease the amount of REMERON RD® you, or those in your care if you are a caregiver or guardian, are taking unless your doctor tells you to, and do not stop taking this medication without consulting your doctor (see Warnings and Precautions when taking REMERON RD®).
- Some symptoms may begin to improve within about two weeks, but significant improvement can take several weeks. Continue to follow the doctor's instructions.
- The tablets should be taken at the same time each day, preferably as a single evening dose (prior to sleep). Do not chew them.
- Keep taking your tablets until the doctor tells you to stop. The doctor may tell you to take your medicine for several months. Continue to follow the doctor's instructions.
- If you forget to take your evening dose, do not take the missed dose the next morning. Continue treatment in the evening (prior to sleep) with your normal dose.

The tablet(s) should be taken as follows:

- In order to prevent crushing the tablet, do not push against the tablet pocket (Figure A).

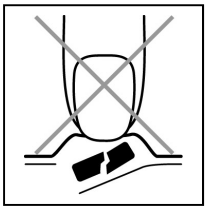

FIGURE A

- Each strip contains six tablet pockets, which are separated by perforations. Bend the strip as indicated. Tear off one tablet pocket along the dotted lines (Figure 1).

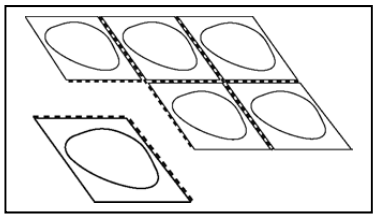

FIGURE 1

- Carefully peel off the lidding foil, starting in the corner indicated by the arrow (Figures 2 and 3).

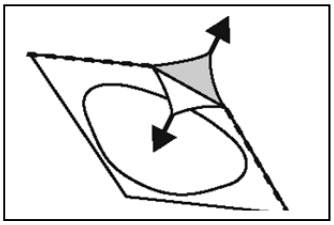

FIGURE 2

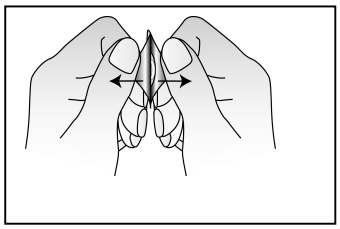

FIGURE 3

- Take out the tablet (making sure your hands are dry) and place it on the tongue (Figure 4). The tablet will rapidly disintegrate and can be swallowed without water.

FIGURE 4

- The tablet should be used immediately after removal from its blister; once removed, it cannot be stored.
- Do not attempt to split the tablet.

Overdose:

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

The most likely signs of an overdose of REMERON® (without other medicines or alcohol) are drowsiness, disorientation and increased heart rate. The symptoms of a possible overdose may include changes to your heart rhythm (fast, irregular heartbeat) and/or fainting which could be symptoms of a life-threatening condition known as Torsade de Pointes.

Missed Dose:

Do not take a double dose to make up for forgotten doses. If you forget to take your evening dose, do not take the missed dose the next morning. Continue treatment in the evening (prior to sleep) with your normal dose.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like other medications, REMERON RD® can cause some side effects. You may not experience any of them. For most patients, side effects are likely to be minor and temporary. However, some may be serious. Some of these side effects may be dose related. Consult your doctor if you experience these or other side effects, as the dose may have to be adjusted.

These are not all the possible side effects you may feel when taking REMERON RD®. If you experience any side effects not listed here, contact your healthcare professional.

- The most common side effects (>10%) include sleepiness, dry mouth, increased appetite, constipation and weight gain.

- Other side effects may include: tiredness (feeling weak); swelling (typically in ankles or feet); occasional dizziness or faintness (especially when you get up quickly from a lying or sitting position); itchiness; tremor (shakiness); abnormal dreams; rash; increased levels of fats in the blood; urinary tract infections; abnormal sensation in the skin (e.g., burning, stinging, tickling or tingly).

Decrease in White Blood Cells

If you experience sudden unexplainable signs of infection such as high fever, chills, sore throat and mouth or nose sores, tell your doctor right away. In rare cases, REMERON RD® can cause a decrease in white blood cells, which are needed to fight infection.

New or Worsened Emotional or Behavioural Problems

A small number of patients taking drugs of this type may feel worse instead of better; for example, they may experience new or worsened feelings of agitation, hostility or anxiety, or thoughts about suicide. Your doctor should be informed of such changes immediately. Close observation by a doctor is necessary in this situation. Do not discontinue your medication on your own. See also the WARNINGS AND PRECAUTIONS section.

Discontinuation Symptoms

Contact your doctor before stopping or reducing your dosage of REMERON RD®. Symptoms such as dizziness, abnormal dreams, electric shock sensations, agitation, anxiety, difficulty concentrating, headache, tremor, nausea, vomiting, sweating and other symptoms have been reported after stopping REMERON RD®. These symptoms usually disappear without needing treatment. Tell your doctor immediately if you have these or any other symptoms. Your doctor may adjust the dosage of REMERON RD® to alleviate the symptoms. See WARNINGS AND PRECAUTIONS section for more information.

Effects on Newborns

Some newborns whose mothers took an SSRI or other newer antidepressants during pregnancy have shown such symptoms as breathing and feeding difficulties, jitteriness and constant crying. If your baby experiences any of these symptoms, contact your doctor as soon as you can. See WARNINGS AND PRECAUTIONS section for more information.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom/effect		Talk with your doctor or pharmacist		Seek immediate emergency medical assistance
		Only if severe	In all cases	
Common	Drowsiness which can lead to impaired concentration, generally occurring during the first few weeks of treatment	√		
	Weight gain	√		
Infrequent	Aggression			√
Rare	Bruising and/or unusual bleeding and symptoms of infection such as sudden high fever, sore throat, mouth ulcers, severe digestive system disturbances or other signs of infection (symptoms of blood cell disturbances).		√	
	Convulsions (loss of consciousness with uncontrollable shaking)			√
	Fainting/loss of consciousness		√	
	Nightmares/vivid dreams, agitation or confusion		√	
	Hallucinations (strange visions or sounds)		√	
	Mania (excessive happiness or irritability, racing thoughts, greatly increased energy, severe trouble sleeping, reckless behaviour)			√
	Akathisia (feeling restless and unable to stand still)	√		

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom/effect		Talk with your doctor or pharmacist		Seek immediate emergency medical assistance
		Only if severe	In all cases	
	Uncontrolled, sudden movements	√		
	Restless legs (feeling of unrest during night mainly located in the legs combined with sudden muscle contractions in the legs)	√		
	Pain in the joints or muscles		√	
	Jaundice (yellowing of eyes or skin; dark urine			√
	Symptoms of depression (anxiety and disturbed sleep)	√		
	Severe skin reactions such as Stevens-Johnson syndrome (fever, rash, swollen lymph nodes, hives, sore mouth, sore eyes or swelling of lips or tongue)			√
	Low sodium levels in blood (feeling ill with symptoms of weakness, drowsiness, confusion, combined with achy, stiff or uncoordinated muscles)			√
	Abdominal pain and nausea; this may suggest inflammation of the pancreas (pancreatitis)	√		

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom/effect		Talk with your doctor or pharmacist		Seek immediate emergency medical assistance
		Only if severe	In all cases	
Very Rare	A combination of symptoms such as unexplainable fever, sweating, increased heart rate, diarrhea, (uncontrollable) muscle contractions, shivering, overactive reflexes, restlessness, mood changes and unconsciousness (can be signs of serotonin syndrome)			√
See WARNINGS & PRECAUTIONS	Changes in feelings or behaviour (anger, anxiety, suicidal or violent thoughts)			√
Unknown	Abnormal heart rate or rhythm, palpitations, fainting		√	
	Rhabdomyolysis (very dark ("tea coloured") urine, muscle tenderness and/or aching)		√	

This is not a complete list of side effects. For any unexpected effects while taking REMERON RD®, contact your doctor or pharmacist.

HOW TO STORE IT

- Store at controlled room temperature, 15°C - 30°C in the original package. Protect from light and moisture. Use immediately upon opening individual tablet blister.
- Keep REMERON RD® out of the reach and sight of children.
- Do not use REMERON RD® after the expiry date indicated on the package.

REPORTING SIDE EFFECTS

You can help improve the safe use of health products for Canadians by reporting serious and unexpected side effects to Health Canada. Your report may help to identify new side effects and change the product safety information.

3 ways to report:

- Online at MedEffect;
- By calling 1-866-234-2345 (toll-free);
- By completing a Consumer Side Effect Reporting Form and sending it by:
  - Fax to 1-866-678-6789 (toll-free), or
  - Mail to: Canada Vigilance Program
    Health Canada, Postal Locator 1908C
    Ottawa, ON
    K1A 0K9

    Postage paid labels and the Consumer Side Effect Reporting Form are available at MedEffect.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice. »

MORE INFORMATION

If you want more information about REMERON RD®:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Consumer Information by visiting the Health Canada website or Merck Canada web site www.merck.ca or by calling Merck Canada at 1-800-567-2594

To report an adverse event related to REMERON RD®, please contact 1-800-567-2594.

This leaflet was prepared by Merck Canada Inc.

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