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

Mirtazapine is a highly selective, high-affinity, and long-acting agonist at the 5-HT2B/2C and 5-HT3 receptors. Mirtazapine is approximately 85% bound to plasma proteins.

Mirtazapine is extensively metabolized after oral administration. Plasma levels are linearly related to dose over a dose range of 5 to 75 mg/day. In patients with moderate hepatic impairment, mirtazapine half-life of 37 hours for females vs. 26 hours for males (see CLINICAL PHARMACOLOGY).

Mirtazapine is a substrate for CYP2D6 and is also a weak inhibitor of CYP2D6. Mirtazapine is a substrate of UGT1A4 (see DRUG INTERACTIONS).

Mirtazapine is highly protein bound, and after a single oral dose, mirtazapine is approximately 98% protein bound and increases to approximately 99% protein bound in patients with reduced renal function.

Mirtazapine is metabolized via the liver and is excreted mainly in the urine. The main metabolite of mirtazapine is nor-mirtazapine. Mirtazapine and desmethylmirtazapine are the major plasma peaks after ingestion of mirtazapine. The elimination half-life of desmethylmirtazapine is longer than that of mirtazapine.

Mirtazapine has not been shown to be addictive in patients in long-term studies. However, in patients who discontinue REMERON immediately after long-term treatment, withdrawal symptoms (e.g., agitation or irritability) may occur and patients should be closely monitored in these situations.

Mirtazapine is primarily distributed in the central nervous system (CNS) with a very low cerebrospinal fluid/plasma ratio. After multiple doses, the cerebrospinal fluid/plasma ratio is approximately 0.6. Mirtazapine concentrations in plasma and cerebrospinal fluid are related to dose.

Mirtazapine is almost completely absorbed following oral administration. The mean absolute bioavailability of mirtazapine in healthy volunteers is approximately 85%.

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The electrocardiograms for 338 patients who received REMERON® (mirtazapine) Tablets were analyzed. The electrocardiograms were recorded before administration of the first dose of REMERON®, before rechallenge when the drug was discontinued, and after rechallenge when the drug was restarted. The data from these evaluations revealed a higher incidence of ECG changes with REMERON® compared to placebo. The incidence of ECG changes with REMERON® varied in different trials, and the changes were transient. The electrocardiograms were recorded using a standard 12-lead electrocardiogram system. The mean heart rate was increased, up to a mean rate of 4.8 bpm at the end of treatment in REMERON®-treated patients compared to placebo at the end of treatment. The mean increase in heart rate was 1.68 bpm for placebo and 2.74 bpm for REMERON®.

The rate of ECG changes was not significantly different between REMERON® and placebo. However, there were differences in the types of changes observed. The incidence of ECG changes with REMERON® was higher than with placebo in the following categories:

- **Increased QTc interval**: REMERON® had an incidence of 1.0% compared to placebo's 0.2%.
- **Decreased QTc interval**: REMERON® had an incidence of 0.1% compared to placebo's 0.0%.
- **Prolongation of QT interval**: REMERON® had an incidence of 0.1% compared to placebo's 0.0%.
- **Arrhythmias**: REMERON® had an incidence of 0.1% compared to placebo's 0.0%.
- **Sinus bradycardia**: REMERON® had an incidence of 0.1% compared to placebo's 0.0%.

The changes observed in REMERON®-treated patients were not considered to be clinically significant. The magnitude of these changes was not always predictive of human response, this drug should be used with caution and in small doses in patients with underlying conduction system diseases.

In conclusion, Mirtazapine was associated with an increase in heart rate, but this was not considered to be clinically significant. The incidence of ECG changes with REMERON® was lower than with placebo in the following categories:

- **Decreased QTc interval**: REMERON® had an incidence of 0.1% compared to placebo's 0.0%.
- **Prolongation of QT interval**: REMERON® had an incidence of 0.1% compared to placebo's 0.0%.
- **Arrhythmias**: REMERON® had an incidence of 0.1% compared to placebo's 0.0%.
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