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Mitzap™

(Mirtazapine)

TABLET

مِٹزیپ

COMPOSITION:
Mitzap Tablet 15 mg:
Each film coated tablet contains:
Mirtazapine ..... 15 mg.

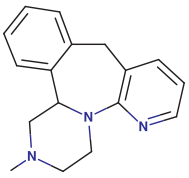
Product Specs.: USP

Mitzap Tablet 30 mg:
Each film coated tablet contains:
Mirtazapine ..... 30 mg.

Product Specs.: USP

WARNING:
SUICIDAL THOUGHTS AND BEHAVIORS
See full prescribing information for complete boxed warning.
Increased risk of suicidal thoughts and behavior in pediatric and young adult patients taking antidepressants. Closely monitor all antidepressant-treated patients for clinical worsening and emergence of suicidal thoughts and behaviors. Mirtazapine tablet is not approved for use in pediatric patients. Closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. Mirtazapine is not approved for use in pediatric patients.

DESCRIPTION:
Mirtazapine Tablets are an orally administered drug. Mirtazapine has a tetra-cyclic chemical structure and belongs to the piperazino-azepine group of compounds. It is designated 1,2,3,4,10,14b-hexahydro-2-methylpyrazino [2,1-a] pyrido [2,3-c] benzazepine and has the empirical formula of $C_{17}H_{19}N_3$. Its molecular weight is 265.36. The structural formula is the following and it is the racemic mixture:



CLINICAL PHARMACOLOGY:
Pharmacodynamics:
The mechanism of action of Mirtazapine 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 auto receptors and heteroreceptors, an action that is postulated to result in an increase in central noradrenergic and serotonergic activity. Mirtazapine is a potent antagonist of 5-HT2 and 5-HT3 receptors. Mirtazapine has no significant affinity for the 5-HT1A and 5-HT1B receptors. Mirtazapine is a potent antagonist of histamine (H1) receptors, a property that may explain its prominent sedative effects. Mirtazapine is a moderate peripheral α1 adrenergic antagonist, a property that may explain the occasional orthostatic hypotension reported in association with its use. Mirtazapine is a moderate antagonist at muscarinic receptors, a property that may explain the relatively low incidence of anticholinergic side effects associated with its use.

Pharmacokinetics:
Mirtazapine Tablets are rapidly and completely absorbed following oral administration and have a half-life of about 20 to 40 hours. Peak plasma concentrations are reached within about 2 hours following an oral dose. The presence of food in the stomach has a minimal effect on both the rate and extent of absorption and does not require a dosage adjustment. Mirtazapine is extensively metabolized after oral administration. Major pathways of biotransformation are demethylation and hydroxylation followed by glucuronide conjugation. In vitro data from human liver microsomes indicate that cytochrome 2D6 and 1A2 are involved in the formation of the 8¬ hydroxy metabolites of Mirtazapine, whereas cytochrome 3A is considered to be responsible for the formation of the N-desmethyl and N-oxide metabolite. Mirtazapine has an absolute bioavailability of about 50%. It is eliminated predominantly via urine (75%) with 15% in feces. Several unconjugated metabolites possess pharmacological activity but are present in the plasma at very low levels. The (–) enantiomer has an elimination half-life that is approximately twice as long as the (+) enantiomer and therefore achieves plasma levels that are about 3 times as high as that of the (+) enantiomer. Plasma levels are linearly related to dose over a dose range of 15 to 80 mg. The mean elimination halflife of Mirtazapine after oral administration ranges from approximately 20 to 40 hours across age and gender subgroups, with females of all ages exhibiting significantly longer elimination half-lives than males (mean half-life of 37 hours for females vs. 26 hours for males). Steady state plasma levels of Mirtazapine are attained within 5 days, with about 50% accumulation (accumulation ratio = 1.5). Mirtazapine is approximately 85% bound to plasma proteins over a concentration range of 0.01 to 10 mcg/mL.
Metabolism and excretion: Following a single oral dose of 14C labeled olanzapine, 7% of the dose of olanzapine was recovered in the urine as unchanged drug, indicating that olanzapine is highly metabolized. Approximately of the dose was recovered in the urine and feces, respectively. In the plasma, olanzapine accounted for only 12% of the AUC for total radioactivity, indicating significant exposure to metabolites. After multiple dosing, the major circulating metabolites were the 10-N-glucuronide, present at steady state at 44% of the concentration of olanzapine, and 4´-N-desmethyl olanzapine, present at steady state at 31% of the concentration of olanzapine. Both metabolites lack pharmacological activity at the concentrations observed. Direct glucuronidation and cytochrome P450 (CYP) mediated oxidation are the primary metabolic pathways for olanzapine. In vitro studies suggest that CYPs 1A2 and 2D6, and the flavin-containing monooxygenase system are involved in olanzapine oxidation. CYP2D6 mediated oxidation appears to be a minor metabolic pathway in vivo, because the clearance of olanzapine is not reduced in subjects who are deficient in this enzyme.
Special Populations:
Pregnancy: Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during Mirtazapine therapy.

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Nursing mothers: Patients should be advised to notify their physician if they are breast-feeding an infant.
Renal impairment: The disposition of Mirtazapine was studied in patients with varying degrees of renal function. Elimination of Mirtazapine is correlated with creatinine clearance. Total body clearance of Mirtazapine was reduced approximately 30% in patients with moderate (Sclcr = 11–39 mL/min/1.73 M²) and approximately 50% in patients with severe (Sclcr = <10 mL/min/1.73 M²) renal impairment when compared to normal subjects. Caution is indicated in administering Mirtazapine to patients with compromised renal function.
Hepatic impairment: Following a single 15-mg oral dose of Mirtazapine, the oral clearance of Mirtazapine was decreased by approximately 30% in hepatically impaired patients compared to subjects with normal hepatic function. Caution is indicated in administering Mirtazapine to patients with compromised hepatic function.
Pediatric use: Safety and effectiveness of Mirtazapine in the pediatric population have not been established.
Geriatric use: Following oral administration of Mirtazapine Tablets 20 mg/day for 7 days to subjects of varying ages (range, 25–74), oral clearance of Mirtazapine was reduced in the elderly compared to the younger subjects. The differences were most striking in males, with a 40% lower clearance in elderly males compared to younger males, while the clearance in elderly females was only 10% lower compared to younger females. Caution is indicated in administering Mirtazapine to elderly patients.

INDICATIONS AND USAGE:
Mirtazapine Tablets are indicated for the treatment of major depressive disorder. The efficacy of Mirtazapine in the treatment of major depressive disorder was established in 6-week controlled trials of outpatients whose diagnoses corresponded most closely to the Diagnostic and Statistical Manual of Mental Disorders – 3rd edition (DSM-III) category of major depressive disorder. A major depressive episode (DSM-IV) implies a prominent and relatively persistent (nearly every day for at least 2 weeks) depressed or dysphoric mood that usually interferes with daily functioning, and includes at least 5 of the following 9 symptoms: depressed mood, loss of interest in usual activities, significant change in weight and/or appetite, insomnia or hypersomnia, psychomotor agitation or retardation, increased fatigue, feelings of guilt or worthlessness, slowed thinking or impaired concentration, a suicide attempt, or suicidal ideation. The effectiveness of Mirtazapine in hospitalized depressed patients has not been adequately studied. The efficacy of Mirtazapine in maintaining a response in patients with major depressive disorder for up to 40 weeks following 8 to 12 weeks of initial open-label treatment was demonstrated in a placebo-controlled trial. Nevertheless, the physician who elects to use Mirtazapine for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient

DOSAGE AND ADMINISTRATION:
Starting Dose: 15-mg once daily; may increase up to maximum recommended dose of 45 mg once daily.
- Administer orally once daily, preferably in the evening prior to sleep.
- Administer Mirtazapine tablet immediately after removal from blister pack.
- Reduce dose gradually when discontinuing Mirtazapine tablet.

CONTRAINDICATIONS:
Hypersensitivity: Mirtazapine tablets are contraindicated in patients with a known hypersensitivity to Mirtazapine or to any of the excipients.
Monoamine oxidase inhibitors: The concomitant use of Mirtazapine tablets and a monoamine oxidase (MAO) inhibitor is contraindicated. Mirtazapine should not be used within 14 days of initiating or discontinuing therapy with a monoamine oxidase inhibitor (MAOI).

WARNINGS AND PRECAUTIONS:
- ***Agranulocytosis:*** If sore throat, fever, stomatitis or signs of infection occur, along with a low white blood cell count, treatment with Mirtazapine tablet should be discontinued and the patient should be closely monitored.
- ***Serotonin Syndrome:*** Increased risk when co-administered with other serotonergic drugs (e.g., SSRI, SNRI, triptans), but also when taken alone. If it occurs, discontinue Mirtazapine tablet and initiate supportive treatment.
- ***Angle-Closure Glaucoma:*** Angle closure glaucoma has occurred in patients with untreated anatomically narrow angles treated with antidepressants.
- ***QTc Prolongation:*** Use Mirtazapine tablet with caution in patients with risk factors for QTc prolongation.
- ***Increased Appetite/Weight Gain:*** Mirtazapine tablet has been associated with increased appetite and weight gain.
- ***Somnolence:*** May impair judgment, thinking and/or motor skills. Use with caution when engaging in activities requiring alertness, such as driving or operating machinery.
- ***Activation of Mania/Hypomania:*** Screen patients for bipolar disorder prior to initiating treatment.
- ***Seizures:*** Use with caution in patients with a seizure disorder.
- ***Elevated Cholesterol/Triglycerides:*** Has been reported with Mirtazapine use.
- ***Hyponatremia:*** May occur as a result of treatment with serotonergic antidepressants, including Mirtazapine tablet.
- ***Transaminase Elevations:*** Clinically significant elevations have occurred. Use with caution in patients with impaired hepatic function.

ADVERSE REACTIONS:
Most common adverse reactions (⩾5% or greater and twice placebo) were somnolence, increased appetite, weight gain, and dizziness

DRUG INTERACTIONS:
Strong CYP3A inducers: Dosage increase may be needed for Mirtazapine tablet with concomitant use of strong CYP3A inducers.
- ***Strong CYP3A inhibitors:*** Dosage decrease may be needed when Mirtazapine tablet is co-administered with strong CYP3A inhibitors.
- ***Cimetidine:*** Dosage decrease may be needed when Mirtazapine tablet is co-administered with cimetidine.
- ***Warfarin:*** Monitor INR during concomitant use.

INSTRUCTIONS:
- Store below 30°C.
- Protect from heat, sunlight & moisture.
- Keep out of the reach of children.
- To be sold on the prescription of a registered medical practitioner only.

PRESENTATION:

Mitzap Tablet 15 mg	:	Pack of 2 x 10 tablets.
Mitzap Tablet 30 mg	:	Pack of 2 x 10 tablets.

ہدایات:
۳۰ درجہ سینٹی گریڈ سے کم درجہ حرارت پر رکھیں۔
گرمی، دھوپ اور نمی سے بچائیں۔
بچوں کی پہنچ سے دور رکھیں۔
صرف مستند ڈاکٹر کے نسخے پر فروخت کریں۔

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