

**What are the possible side effects of mirtazapine tablets?****Mirtazapine tablets may cause serious side effects, including:**

- See, “**What is the most important information I should know about mirtazapine tablets?**”

- **Low white blood cell count.** Tell your healthcare provider right away if you develop any signs or symptoms of a low white blood cell count, including:

- fever
- sore throat
- flu-like symptoms
- chills
- mouth or nose sores
- infections

- **Serotonin syndrome.** A potentially life-threatening problem called serotonin syndrome can happen when you take mirtazapine tablets with certain other medicines. See, “**Who should not take mirtazapine tablets?**” Stop taking mirtazapine tablets and call your healthcare provider or go to the nearest hospital emergency room right away if you have any of the following signs and symptoms of serotonin syndrome:

- agitation
- confusion
- fast heart beat
- dizziness
- flushing
- tremors, stiff muscles, or muscle twitching
- seizures
- seeing or hearing things that are not real (hallucinations)
- coma
- blood pressure changes
- sweating
- high body temperature (hyperthermia)
- loss of coordination
- nausea, vomiting, diarrhea

- **Eye problems (angle-closure glaucoma).** Mirtazapine tablets may cause a certain type of eye problem called angle-closure glaucoma. Call your healthcare provider if you have eye pain, changes in your vision, or swelling or redness in or around the eye. Only some people are at risk for these problems. You may want to undergo an eye examination to see if you are at risk and receive preventative treatment if you are.

- **Heart rhythm problems.**

- **Severe skin reaction.** Mirtazapine tablets may cause a severe skin reaction that may include rash, fever, swollen glands, and other organ involvement such as liver, kidney, lung and heart. The reaction may sometimes be fatal. Tell your healthcare provider right away if you experience any of these signs.

- **Increased appetite and weight gain.**

- **Sleepiness.** See, “**What should I avoid while taking mirtazapine tablets?**”

- **Mania or hypomania (manic episodes)** in people who have a history of bipolar disorder. Symptoms may include:

- greatly increased energy
- racing thoughts
- unusually grand ideas
- talking more or faster than usual
- severe trouble sleeping
- reckless behavior
- excessive happiness or irritability

- **Seizures (convulsions).**

- **Increased fat levels (cholesterol and triglycerides) in your blood.**

- **Low sodium levels in your blood (hyponatremia).** Low sodium levels in your blood may be serious and may cause death. Elderly people may be at greater risk for this. Signs and Symptoms of low sodium levels in your blood may include:

- headache
- memory changes
- weakness and unsteadiness on your feet which can lead to falls
- difficulty concentrating
- confusion

In severe or more sudden cases, signs and symptoms include:

- hallucinations (seeing or hearing things that are not real)
- seizures
- respiratory arrest
- fainting
- coma
- death

- **Changes in liver function tests.**

- **Discontinuation syndrome.** Suddenly stopping mirtazapine tablets may cause you to have serious side effects. Your healthcare provider may want to decrease your dose slowly. Symptoms may include:

- dizziness
- irritability and agitation
- anxiety
- sweating
- seizures
- ringing in your ears (tinnitus)
- nausea and vomiting
- problems sleeping
- tiredness
- confusion
- electric shock sensation (paresthesia)
- shaking (tremor)
- headache
- abnormal dreams
- changes in your mood
- hypomania

The most common side effects of mirtazapine tablets include:

- sleepiness
- increased appetite
- weight gain
- dizziness

These are not all the possible side effects of mirtazapine tablets.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store mirtazapine tablets?

- Store mirtazapine tablets at room temperature between 68°F to 77°F (20°C to 25°C).

- Keep mirtazapine tablets away from light and moisture.

Keep mirtazapine tablets, and all medicines out of the reach of children.**General information about the safe and effective use of mirtazapine tablets.**

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use mirtazapine tablets for a condition for which it was not prescribed. Do not give mirtazapine tablets to other people, even if they have the same symptoms that you have. They may harm them. You can ask your healthcare provider or pharmacist for information about mirtazapine tablets that is written for healthcare professionals.

What are the ingredients in mirtazapine tablets?

Active ingredient: mirtazapine, USP

Inactive ingredients: colloidal silicon dioxide, corn starch, hydroxypropyl methyl cellulose, iron oxide red (for 30 mg only), iron oxide yellow (for 15 mg and 30 mg only), lactose monohydrate, magnesium stearate, polyethylene glycol, titanium dioxide.

Medication Guide available at <http://camberpharma.com/medication-guides>

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the formation of the N-desmethyl and N-oxide metabolite. Several unconjugated metabolites possess pharmacological activity but are present in the plasma at very low levels.

Excretion

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

Specific Populations.**Geriatric Patients**

Following oral administration of mirtazapine tablets 20 mg/day for 7 days to subjects of varying ages (range 25 to 74 years old), oral clearance of mirtazapine was reduced in the elderly compared to the younger subjects. The clearance in elderly males was 40% lower compared to younger males, while the clearance was 10% lower in elderly females compared to younger females (see **Warnings and Precautions (5.15), Use in Specific Populations (8.5)**).

Male and Female Patients

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

Race

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

Patients with Renal Impairment

When compared to subjects with normal renal function, total body clearance of mirtazapine was reduced approximately 30% in renal impaired patients with GFR=11 to 20 mL/min/1.73 m² and approximately 50% in renal impaired patients with GFR<10 mL/min/1.73 m² (see **Warnings and Precautions (5.15), Use in Specific Populations (8.6)**).

Patients with Hepatic Impairment

Following a single 15 mg oral dose of mirtazapine tablets, the oral clearance of mirtazapine in patients with hepatic impairment was decreased by approximately 30%, compared to subjects with normal hepatic function (see **Warnings and Precautions (5.13, 5.15), Use in Specific Populations (8.6)**).

Drug Interactions Studies.**Warfarin**

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

QTc-Prolonging Drugs

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

Phenytin

In healthy male subjects (n=18), phenytoin (200 mg daily, at steady state) increased mirtazapine (20 mg daily, at steady state) clearance about 2-fold, resulting in a decrease in average plasma mirtazapine concentrations of 45% (see **Drug Interactions (7)**). Mirtazapine did not significantly affect the pharmacokinetics of phenytoin.

Carbamazepine

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

Cimetidine

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

Ketobonazole

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

Amiripryline

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

Paroxetine

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

Lithium

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

Risperidone

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

Alcohol

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

Diazepam

Concomitant administration of diazepam (15 mg) had a minimal effect on plasma levels of mirtazapine (15 mg) in 12 healthy subjects. However, the impairment of motor skills produced by mirtazapine tablets has been shown to be additive with those caused by diazepam.

13 NONCLINICAL TOXICOLOGY**13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility****Carcinogenesis.**

Carcinogenicity studies were conducted with mirtazapine given in the diet at doses of 2, 20, and 200 mg/kg/day to mice and 2, 20, and 60 mg/kg/day to rats. The highest doses used are approximately 20 and 12 times the maximum recommended human dose (MRHD) of 45 mg/day, based on body surface area (mg/m²) in mice and rats, respectively. There was an increased incidence of hepatocellular adenoma and carcinoma in male mice at the high dose. In rats, there was an increase in hepatocellular adenoma in females at the mid and high doses and in hepatocellular tumors and thyroid follicular adenoma/cyadenomas and carcinoma in males at the high dose.

Mutagenesis.

Mirtazapine was not mutagenic or clastogenic and did not induce general DNA damage as determined in several genotoxicity tests: Ames test, *in vitro* gene mutation assay in Chinese hamster V79 cells, *in vitro* sister chromatid exchange assay in cultured rabbit lymphocytes, *in vivo* bone marrow micronucleus test in rats, and unscheduled DNA synthesis assay in HeLa cells.

Impairment of Fertility.

In a fertility study in rats, mirtazapine was given at doses up to 100 mg/kg (20 times the maximum recommended human dose (MRHD), based on body surface area (mg/m²)). Mating and conception were not affected by the drug, but estrous cycling was disrupted at doses that were 3 or more times the MRHD, and pre-implantation losses occurred at 20 times the MRHD.

14 CLINICAL STUDIES

The efficacy of mirtazapine tablets as a treatment for major depressive disorder was established in 4 placebo-controlled, 6-week trials in adult outpatients meeting DSM-III criteria for major depressive disorder. Patients were titrated with mirtazapine tablets from a dose range of 5 mg to 35 mg/day. The mean mirtazapine dose for patients who completed these 4 studies ranged from 21 to 32 mg/day. Overall, these studies demonstrated mirtazapine tablets to be superior to placebo on at least 5 of the following 4 measures: 21-Item Hamilton Depression Rating Scale (HDRS) total score; HDRS Depressed Mood Item; CGI Severity score; and Montgomery-Åsberg Depression Rating Scale (MADRS). Superiority of mirtazapine tablets over placebo was also found for certain factors of the HDRS, including anhedonia/loss of interest and sleep disturbance factor. Examination of age and gender subsets of the population did not reveal any differential responsiveness on the basis of these subgroups.

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 mirtazapine tablets were randomized to continuation of mirtazapine tablets or placebo for up to 40 weeks of observation for relapse. Response during the open phase was defined as having achieved a HAM-D 17 total score of ≤9 and a CGI-Improvement score of 1 or 2 at 2 consecutive visits beginning with week 6 of the 8 to 12 weeks in the open-label phase of the study. Relapse during the double-blind phase was determined by the individual investigators. Patients receiving continued mirtazapine tablets treatment experienced significantly lower relapse rates over the subsequent 40 weeks compared to those receiving placebo. This pattern was demonstrated in both male and female patients.

16 HOW SUPPLIED/STORAGE AND HANDLING

Mirtazapine tablets, USP are supplied as:

7.5 mg Tablets – White, round biconvex tablets debossed with ‘E14’ on one side, plain on the other side.

Bottles of 30 NDC 31722-407-30

Bottles of 500 NDC 31722-407-05

15 mg Tablets – Yellow colored, oval shape biconvex tablets debossed with ‘E’ and ‘15’ separated with functionally scored line on one side, plain on the other side.

Bottles of 30 NDC 31722-408-30

Bottles of 500 NDC 31722-408-05

Bottles of 1000 NDC 31722-408-10

30 mg Tablets – Red-brown colored, oval shape biconvex tablets debossed with ‘E’ and ‘16’ separated with functionally scored line on one side, plain on the other side.

Bottles of 30 NDC 31722-409-30

Bottles of 500 NDC 31722-409-05

45 mg Tablets – White, oval shape biconvex tablets debossed with ‘E17’ on one side, plain on the other side.

Bottles of 30 NDC 31722-410-30

Bottles of 500 NDC 31722-410-05

Storage.

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

17 PATIENT COUNSELING INFORMATION

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

Suicidal Thoughts and Behaviors

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

Aggravated Infection

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

Serotonin Syndrome

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

QT Prolongation and Torsades de Pointes

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

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS).

Advise patients to report to their healthcare provider at the earliest onset of fever, rash, swollen lymph nodes, or other signs and symptoms suggestive of Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) (see **Contraindications (4), Warnings and Precautions (5.6)**).

Somnolence.

Advise patients that mirtazapine tablets may impair judgment, thinking, and particularly, motor skills, because of its prominent sedative effect. Caution patients about performing activities requiring mental alertness, such as operating hazardous machinery or operating a motor vehicle, until they are reasonably certain that mirtazapine tablets therapy does not adversely affect their ability to engage in such activities. (see **Warnings and Precautions (5.8)**).

Alcohol.

Advise patients to avoid alcohol while taking mirtazapine tablets (see **Warnings and Precautions (5.8), Drug Interactions (7)**).

Activation of Mania/Hypomania.

Advise patients and their caregivers to observe for signs of activation of mania/hypomania and instruct them to report such symptoms to the healthcare provider (see **Warnings and Precautions (5.9)**).

Discontinuation Syndrome.

Advise patients not to abruptly discontinue mirtazapine tablets and to discuss any tapering regimen with their healthcare provider. Adverse reactions can occur when mirtazapine tablets are discontinued (see **Dosage and Administration (2.6), Warnings and Precautions (5.14)**).

Allergic Reactions.

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

Pregnancy.

- Advise patients to notify their physician if they become pregnant or intend to become pregnant during mirtazapine tablets therapy.

Lactation.

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

Angle-Closure Glaucoma.

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

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