MIRTAZAPINE- mirtazapine tablet, orally disintegrating
Watson Laboratories, Inc.

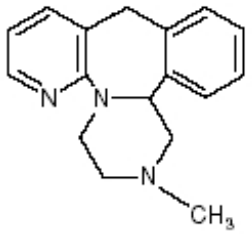
ONCE-A-DAY
Mirtazapine Orally Disintegrating Tablets USP
Two Medication Guides Included

Suicidality and Antidepressant Drugs

Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of mirtazapine orally disintegrating tablets or any other antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction in risk with antidepressants compared to placebo in adults aged 65 and older. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed 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 orally disintegrating tablets are not approved for use in pediatric patients. (See WARNINGS: Clinical Worsening and Suicide Risk, PRECAUTIONS: Information for Patients, and PRECAUTIONS: Pediatric Use)

DESCRIPTION

Mirtazapine orally disintegrating tablets USP are an orally administered drug. Mirtazapine has a tetracyclic chemical structure and belongs to the piperazino-azepine group of compounds. It is designated 1,2,3,4,10,14b-hexahydro-2-methylpyrazino [2,1-a] pyrido [2,3-c] 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:



Mirtazapine is a white to creamy white crystalline powder which is slightly soluble in water. Mirtazapine orally disintegrating tablets are available for oral administration as an orally disintegrating tablet containing 15 or 30 mg of mirtazapine. It disintegrates in the mouth within seconds after placement on the tongue, allowing its contents to be subsequently swallowed with or without water. Mirtazapine orally disintegrating tablets also contain the following inactive ingredients: aspartame powder, colloidal silicon dioxide, crospovidone, magnesium stearate, mannitol, microcrystalline cellulose, natural and artificial orange flavor, sodium stearyl fumarate and xylitol.

CLINICAL PHARMACOLOGY

Pharmacodynamics

The mechanism of action of mirtazapine orally disintegrating 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 α_2 adrenergic inhibitory autoreceptors 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-HT_2 and 5-HT_3 receptors. Mirtazapine has no significant affinity for the 5-HT_{1A} and 5-HT_{1B} receptors.

Mirtazapine is a potent antagonist of histamine (H_1) receptors, a property that may explain its prominent sedative effects.

Mirtazapine is a moderate peripheral α_1 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 orally disintegrating 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 orally disintegrating tablets are bioequivalent to mirtazapine tablets.

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 metabolite 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 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). 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.

Special Populations

<u>Geriatric</u>

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 orally disintegrating tablets to elderly patients (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Pediatrics

Safety and effectiveness of mirtazapine in the pediatric population have not been established (see PRECAUTIONS).

Gender

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) (see Pharmacokinetics).

Race

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

Renal Insufficiency

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 (Clcr = 11–39 mL/min/1.73 m^2) and approximately 50% in patients with severe (Clcr = <10 mL/min/1.73 m^2) renal impairment when compared to normal subjects. Caution is indicated in administering mirtazapine orally disintegrating tablets to patients with compromised renal function (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Hepatic Insufficiency

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 orally disintegrating tablets to patients with compromised hepatic function (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Clinical Trials Showing Effectiveness

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 from a dose range of 5 mg up to 35 mg/day. Overall, these studies demonstrated mirtazapine to be superior to placebo on at least 3 of the following 4 measures: 21-Item Hamilton Depression Rating Scale (HDRS) total score; HDRS Depressed Mood Item; CGI Severity score; and Montgomery and Asberg Depression Rating Scale (MADRS). Superiority of mirtazapine over placebo was also found for certain factors of the HDRS, including anxiety/somatization factor and sleep disturbance factor. The mean mirtazapine dose for patients who completed these 4 studies ranged from 21 to 32 mg/day. A fifth study of similar design utilized a higher dose (up to 50 mg) per day and also showed effectiveness.

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

In a longer-term study, patients meeting (DSM-IV) criteria for major depressive disorder who had responded during an initial 8 to 12 weeks of acute treatment on mirtazapine were randomized to continuation of mirtazapine or placebo for up to 40 weeks of observation for relapse. Response during the open phase was defined as having achieved a HAM-D 17 total score of ≤8 and a CGI-Improvement score of 1 or 2 at 2 consecutive visits beginning with week 6 of the 8 to 12 weeks in the open-label

phase of the study. Relapse during the double-blind phase was determined by the individual investigators. Patients receiving continued mirtazapine 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.

INDICATIONS AND USAGE

Mirtazapine orally disintegrating tablets USP are indicated for the treatment of major depressive disorder.

The efficacy of mirtazapine tablets 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 (see CLINICAL PHARMACOLOGY).

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 orally disintegrating tablets 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 (see CLINICAL PHARMACOLOGY).

CONTRAINDICATIONS

Hypersensitivity

Mirtazapine orally disintegrating 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 orally disintegrating 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) (see WARNINGS, PRECAUTIONS: Drug Interactions, and DOSAGE AND ADMINISTRATION).

WARNINGS

Clinical Worsening and Suicide Risk

Patients with major depressive disorder (MDD), both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior, whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. Suicide is a known risk of depression and certain other psychiatric disorders, and these disorders themselves are the strongest predictors of suicide. There has been a long-standing concern, however, that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients during the early phases of treatment.

Pooled analyses of short-term placebo-controlled trials of antidepressant drugs (SSRIs and others) showed that these drugs increase the risk of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults (ages 18–24) with major depressive disorder (MDD) and other psychiatric disorders. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction in risk with antidepressants compared to placebo in adults aged 65 and older.

The pooled analyses of placebo-controlled trials in children and adolescents with MDD, obsessive compulsive disorder (OCD), or other psychiatric disorders included a total of 24 short-term trials of 9 antidepressant drugs in over 4400 patients. The pooled analyses of placebo-controlled trials in adults with MDD or other psychiatric disorders included a total of 295 short-term trials (median duration of 2 months) of 11 antidepressant drugs in over 77,000 patients. There was considerable variation in risk of suicidality among drugs, but a tendency toward an increase in the younger patients for almost all drugs studied. There were differences in absolute risk of suicidality across different indications, with the highest incidence in MDD. The risk differences (drug vs. placebo), however, were relatively stable within age strata and across indications. These risk differences (drug-placebo difference in the number of cases of suicidality per 1000 patients treated) are provided in Table 1.

Table 1

Age Range	**Drug-Placebo Difference in Number of Cases of Suicidality per 1000 Patients Treated**
Increases Compared to Placebo	
<18	14 additional cases
18-24	5 additional cases
Decreases Compared to Placebo	
25-64	1 fewer case
≥65	6 fewer cases

No suicides occurred in any of the pediatric trials. There were suicides in the adult trials, but the number was not sufficient to reach any conclusion about drug effect on suicide.

It is unknown whether the suicidality risk extends to longer-term use, i.e., beyond several months. However, there is substantial evidence from placebo-controlled maintenance trials in adults with depression that the use of antidepressants can delay the recurrence of depression.

All patients being treated with antidepressants for any indication should be monitored appropriately and observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases.

The following symptoms, anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, and mania, have been reported in adult and pediatric patients being treated with antidepressants for major depressive disorder as well as for other indications, both psychiatric and nonpsychiatric. Although a causal link between the emergence of such symptoms and either the worsening of depression and/or the emergence of suicidal impulses has not been established, there is concern that such symptoms may represent precursors to emerging suicidality.

Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse, or who are experiencing emergent suicidality or symptoms that might be precursors to worsening depression or suicidality, especially if these symptoms are severe, abrupt in onset, or were not part of the patient’s presenting symptoms.

Families and caregivers of patients being treated with antidepressants for major depressive

disorder or other indications, both psychiatric and nonpsychiatric, should be alerted about the need to monitor patients for the emergence of agitation, irritability, unusual changes in behavior, and the other symptoms described above, as well as the emergence of suicidality, and to report such symptoms immediately to health care providers. Such monitoring should include daily observation by families and caregivers. Prescriptions for mirtazapine orally disintegrating tablets should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose.

Screening Patients for Bipolar Disorder

A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed (though not established in controlled trials) that treating such an episode with an antidepressant alone may increase the likelihood of precipitation of a mixed/manic episode in patients at risk for bipolar disorder. Whether any of the symptoms described above represent such a conversion is unknown. However, prior to initiating treatment with an antidepressant, patients with depressive symptoms should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression. It should be noted that mirtazapine orally disintegrating tablets are not approved for use in treating bipolar depression.

Agranulocytosis

In premarketing clinical trials, 2 (1 with Sjögren's Syndrome) out of 2796 patients treated with mirtazapine tablets developed agranulocytosis [absolute neutrophil count (ANC) <500/mm^3 with associated signs and symptoms, e.g., fever, infection, etc.] and a third patient developed severe neutropenia (ANC <500/mm^3 without any associated symptoms). For these 3 patients, onset of severe neutropenia was detected on days 61, 9, and 14 of treatment, respectively. All 3 patients recovered after mirtazapine was stopped. These 3 cases yield a crude incidence of severe neutropenia (with or without associated infection) of approximately 1.1 per thousand patients exposed, with a very wide 95% confidence interval, i.e., 2.2 cases per 10,000 to 3.1 cases per 1000. If a patient develops a sore throat, fever, stomatitis, or other signs of infection, along with a low WBC count, treatment with mirtazapine orally disintegrating tablets should be discontinued and the patient should be closely monitored.

MAO Inhibitors

In patients receiving other drugs for major depressive disorder in combination with a monoamine oxidase inhibitor (MAOI) and in patients who have recently discontinued a drug for major depressive disorder and then are started on an MAOI, there have been reports of serious and sometimes fatal reactions, including nausea, vomiting, flushing, dizziness, tremor, myoclonus, rigidity, diaphoresis, hyperthermia, autonomic instability with rapid fluctuations of vital signs, seizures, and mental status changes ranging from agitation to coma. Although there are no human data pertinent to such an interaction with mirtazapine orally disintegrating tablets, it is recommended that mirtazapine orally disintegrating tablets not be used in combination with an MAOI, or within 14 days of initiating or discontinuing therapy with an MAOI.

Serotonin Syndrome or Neuroleptic Malignant Syndrome (NMS)-like Reactions

The development of a potentially life-threatening serotonin syndrome or Neuroleptic Malignant Syndrome (NMS)-like reactions have been reported with SSRIs, SNRIs, MAOIs, and other serotonergic drugs used as monotherapy, including mirtazapine orally disintegrating tablets, but particularly with concomitant use of serotonergic drugs (including triptans) with drugs which impair metabolism of serotonin (including MAOIs), or with antipsychotics or other dopamine antagonists. Serotonin syndrome symptoms may include mental status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g., hyperreflexia, incoordination) and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea). Serotonin syndrome,

in its most severe form can resemble neuroleptic malignant syndrome, which includes hyperthermia, muscle rigidity, autonomic instability with possible rapid fluctuation of vital signs, and mental status changes. Patients should be monitored for the emergence of serotonin syndrome or NMS-like signs and symptoms.

The concomitant use of mirtazapine orally disintegrating tablets with MAOIs intended to treat depression is contraindicated [*see* CONTRAINDICATIONS].

If concomitant treatment of mirtazapine orally disintegrating tablets with a 5-hydroxytryptamine receptor agonist (triptan) is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases.

The concomitant use of mirtazapine orally disintegrating tablets with serotonin precursors (such as tryptophan) is not recommended.

Treatment with mirtazapine orally disintegrating tablets and any concomitant serotonergic or antidopaminergic agents, including antipsychotics, should be discontinued immediately if the above events occur and supportive symptomatic treatment should be initiated.

PRECAUTIONS

General

Discontinuation Symptoms

There have been reports of adverse reactions upon the discontinuation of mirtazapine/mirtazapine orally disintegrating 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. The majority of the reported cases are mild and self-limiting. Even though these have been reported as adverse reactions, it should be realized that these symptoms may be related to underlying disease.

Patients currently taking mirtazapine should NOT discontinue treatment abruptly, due to risk of discontinuation symptoms. At the time that a medical decision is made to discontinue treatment with mirtazapine, a gradual reduction in the dose, rather than an abrupt cessation, is recommended.

Akathisia/Psychomotor Restlessness

The use of antidepressants has 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.

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.

Somnolence

In US controlled studies, somnolence was reported in 54% of patients treated with mirtazapine tablets, compared to 18% for placebo and 60% for amitriptyline. In these studies, somnolence resulted in discontinuation for 10.4% of mirtazapine-treated patients, compared to 2.2% for placebo. It is unclear whether or not tolerance develops to the somnolent effects of mirtazapine. Because of the potentially significant effects of mirtazapine on impairment of performance, patients should be cautioned about engaging in activities requiring alertness until they have been able to assess the drug’s effect on their

own psychomotor performance (see Information for Patients).

Dizziness

In US controlled studies, dizziness was reported in 7% of patients treated with mirtazapine, compared to 3% for placebo and 14% for amitriptyline. It is unclear whether or not tolerance develops to the dizziness observed in association with the use of mirtazapine.

Increased Appetite/Weight Gain

In US controlled studies, appetite increase was reported in 17% of patients treated with mirtazapine, compared to 2% for placebo and 6% for amitriptyline. In these same trials, weight gain of ≥7% of body weight was reported in 7.5% of patients treated with mirtazapine, compared to 0% for placebo and 5.9% for amitriptyline. In a pool of premarketing US studies, including many patients for long-term, open-label treatment, 8% of patients receiving mirtazapine discontinued for weight gain. In an 8-week-long pediatric clinical trial of doses between 15 to 45 mg/day, 49% of mirtazapine-treated patients had a weight gain of at least 7%, compared to 5.7% of placebo-treated patients (see PRECAUTIONS: Pediatric Use).

Cholesterol/Triglycerides

In US controlled studies, nonfasting cholesterol increases to ≥20% above the upper limits of normal were observed in 15% of patients treated with mirtazapine, compared to 7% for placebo and 8% for amitriptyline. In these same studies, nonfasting triglyceride increases to ≥500 mg/dL were observed in 6% of patients treated with mirtazapine, compared to 3% for placebo and 3% for amitriptyline.

Transaminase Elevations

Clinically significant ALT (SGPT) elevations (≥3 times the upper limit of the normal range) were observed in 2.0% (8/424) of patients exposed to mirtazapine in a pool of short-term US controlled trials, compared to 0.3% (1/328) of placebo patients and 2.0% (3/181) of amitriptyline patients. Most of these patients with ALT increases did not develop signs or symptoms associated with compromised liver function. While some patients were discontinued for the ALT increases, in other cases, the enzyme levels returned to normal despite continued mirtazapine treatment. Mirtazapine orally disintegrating tablets should be used with caution in patients with impaired hepatic function (see CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION).

Activation of Mania/Hypomania

Mania/hypomania occurred in approximately 0.2% (3/1299 patients) of mirtazapine-treated patients in US studies. Although the incidence of mania/hypomania was very low during treatment with mirtazapine, it should be used carefully in patients with a history of mania/hypomania.

Seizure

In premarketing clinical trials, only 1 seizure was reported among the 2796 US and non-US patients treated with mirtazapine. However, no controlled studies have been carried out in patients with a history of seizures. Therefore, care should be exercised when mirtazapine is used in these patients.

Use in Patients with Concomitant Illness

Clinical experience with mirtazapine orally disintegrating tablets in patients with concomitant systemic illness is limited. Accordingly, care is advisable in prescribing mirtazapine for patients with diseases or conditions that affect metabolism or hemodynamic responses. Mirtazapine orally disintegrating tablets have 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 volunteers. Orthostatic hypotension was infrequently observed in clinical trials with depressed patients. Mirtazapine orally

disintegrating tablets 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).

Mirtazapine clearance is decreased in patients with moderate [glomerular filtration rate (GFR) = 11–39 mL/min/1.73 m^2] and severe [GFR <10 mL/min/1.73 m^2] renal impairment, and also in patients with hepatic impairment. Caution is indicated in administering mirtazapine orally disintegrating tablets to such patients (see CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION).

Information for Patients

Prescribers or other health professionals should inform patients, their families, and their caregivers about the benefits and risks associated with treatment with mirtazapine orally disintegrating tablets and should counsel them in its appropriate use. A patient Medication Guide about “Antidepressant Medicines, Depression and other Serious Mental Illnesses, and Suicidal Thoughts or Actions” is available for mirtazapine orally disintegrating tablets. The prescriber or health professional should instruct patients, their families, and their caregivers to read the Medication Guide and should assist them in understanding its contents. Patients should be given the opportunity to discuss the contents of the Medication Guide and to obtain answers to any questions they may have. The complete text of the Medication Guide is reprinted at the end of this document.

Patients should be advised of the following issues and asked to alert their prescriber if these occur while taking mirtazapine orally disintegrating tablets.

Clinical Worsening and Suicide Risk

Patients, their families, and their caregivers should be encouraged to be alert to the emergence of anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, mania, other unusual changes in behavior, worsening of depression, and suicidal ideation, especially early during antidepressant treatment and when the dose is adjusted up or down. Families and caregivers of patients should be advised to look for the emergence of such symptoms on a day-to-day basis, since changes may be abrupt. Such symptoms should be reported to the patient’s prescriber or health professional, especially if they are severe, abrupt in onset, or were not part of the patient’s presenting symptoms. Symptoms such as these may be associated with an increased risk for suicidal thinking and behavior and indicate a need for very close monitoring and possibly changes in the medication.

Agranulocytosis

Patients who are to receive mirtazapine orally disintegrating tablets should be warned about the risk of developing agranulocytosis. Patients should be advised to contact their physician if they experience any indication of infection such as fever, chills, sore throat, mucous membrane ulceration, or other possible signs of infection. Particular attention should be paid to any flu-like complaints or other symptoms that might suggest infection.

Interference with Cognitive and Motor Performance

Mirtazapine orally disintegrating tablets may impair judgment, thinking, and particularly, motor skills, because of its prominent sedative effect. The drowsiness associated with mirtazapine use may impair a patient’s ability to drive, use machines, or perform tasks that require alertness. Thus, patients should be cautioned about engaging in hazardous activities until they are reasonably certain that mirtazapine orally disintegrating tablets therapy does not adversely affect their ability to engage in such activities.

Completing Course of Therapy

While patients may notice improvement with mirtazapine orally disintegrating tablets therapy in 1 to 4 weeks, they should be advised to continue therapy as directed.

Concomitant Medication

Patients should be advised to inform their physician if they are taking, or intend to take, any prescription or over-the-counter drugs, since there is a potential for mirtazapine orally disintegrating tablets to interact with other drugs.

Alcohol

The impairment of cognitive 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 any dosage form of mirtazapine.

Phenylalanine

Phenylketonuric patients should be informed that mirtazapine orally disintegrating tablets contains phenylalanine 2.6 mg per 15-mg tablet, 5.2 mg per 30-mg tablet.

Pregnancy

Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during mirtazapine orally disintegrating tablets therapy.

Nursing

Patients should be advised to notify their physician if they are breastfeeding an infant.

Laboratory Tests

There are no routine laboratory tests recommended.

Drug Interactions

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 CLINICAL PHARMACOLOGY).

Monoamine Oxidase Inhibitors

(See CONTRAINDICATIONS, WARNINGS, and DOSAGE AND ADMINISTRATION.)

Serotonergic drugs

Based on the mechanism of action of mirtazapine and the potential for serotonin syndrome, caution is advised when mirtazapine orally disintegrating tablets are coadministered with other drugs or agents that may affect the serotonergic neurotransmitter systems, such as tryptophan, triptans, linezolid, serotonin reuptake inhibitors, venlafaxine, lithium, tramadol, or St. John's wort (see CONTRAINDICATIONS and WARNINGS).

Drugs Affecting Hepatic Metabolism

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

Drugs that are Metabolized by and/or Inhibit Cytochrome P450 Enzymes

CYP Enzyme 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 about 2-fold, resulting in a decrease in average plasma mirtazapine concentrations of 45%. Mirtazapine did not significantly affect the pharmacokinetics of phenytoin.

Carbamazepine**:** In healthy male patients (n=24), carbamazepine (400 mg b.i.d.) increased mirtazapine (15

mg b.i.d.) clearance about 2-fold, resulting in a decrease in average plasma mirtazapine concentrations of 60%.

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, 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%. Mirtazapine did not cause relevant changes in the pharmacokinetics of cimetidine. 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), coadministration 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 of mirtazapine by approximately 40% and 50%, respectively.

Caution should be exercised when coadministering 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 cause relevant changes in the pharmacokinetics of steady state paroxetine (40 mg/day), a CYP2D6 inhibitor.

Other Drug-Drug Interactions

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

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 Normalized Ratio (INR) in subjects treated with warfarin. 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 effects of higher doses of lithium on the pharmacokinetics of mirtazapine are unknown.

Risperidone: In an *in vivo*, nonrandomized, interaction study, subjects (n=6) in need of treatment with an antipsychotic and antidepressant drug, showed that mirtazapine (30 mg daily) at steady state did not influence the pharmacokinetics of risperidone (up to 3 mg b.i.d.).

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 were shown to be additive with those produced by alcohol. Accordingly, patients should be advised to avoid alcohol while taking mirtazapine orally disintegrating tablets.

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 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 mirtazapine orally disintegrating tablets.

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 on an mg/m^2 basis in mice and rats, respectively. There was an increased incidence of hepatocellular adenoma and carcinoma in male mice at the high dose. In rats, there was an increase in hepatocellular adenoma in females at the mid and high doses and in hepatocellular tumors and thyroid follicular adenoma/cystadenoma and carcinoma in males at the high dose. 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 high enough to fully characterize the carcinogenic potential of mirtazapine 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 [20 times the maximum recommended human dose (MRHD) on an mg/m^2 basis]. 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.

Pregnancy

Teratogenic Effects – Pregnancy Category C

Reproduction studies in pregnant rats and rabbits at doses up to 100 mg/kg and 40 mg/kg, respectively [20 and 17 times the maximum recommended human dose (MRHD) on an mg/m^2 basis, respectively], have revealed no evidence of teratogenic effects. However, in rats, there was an increase in postimplantation losses in dams treated with mirtazapine. There was an increase in pup deaths during the first 3 days of lactation and a decrease in pup birth weights. The cause of these deaths is not known. The effects occurred at doses that were 20 times the MRHD, but not at 3 times the MRHD, on an mg/m^2 basis. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers

Because some mirtazapine may be excreted in breast milk, caution should be exercised when mirtazapine orally disintegrating tablets are administered to nursing women.

Pediatric Use

Safety and effectiveness in the pediatric population have not been established (see BOXED WARNING and WARNINGS: Clinical Worsening and Suicide Risk). Two placebo-controlled trials in 258 pediatric patients with MDD have been conducted with mirtazapine tablets, and the data were not sufficient to support a claim for use in pediatric patients. Anyone considering the use of mirtazapine orally disintegrating tablets in a child or adolescent must balance the potential risks with the clinical need.

In an 8-week-long pediatric clinical trial of doses between 15 to 45 mg/day, 49% of mirtazapine-treated

patients had a weight gain of at least 7%, compared to 5.7% of placebo-treated patients. The mean increase in weight was 4 kg (2 kg SD) for mirtazapine-treated patients versus 1 kg (2 kg SD) for placebo-treated patients (see PRECAUTIONS: Increased Appetite/Weight Gain).

Geriatric Use

Approximately 190 elderly individuals (≥65 years of age) participated in clinical studies with mirtazapine tablets. This drug is known to be substantially excreted by the kidney (75%), and the risk of decreased clearance of this drug is greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection. Sedating drugs may cause confusion and over-sedation in the elderly. No unusual adverse age-related phenomena were identified in this group. Pharmacokinetic studies revealed a decreased clearance in the elderly. Caution is indicated in administering mirtazapine orally disintegrating tablets to elderly patients (see CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION).

ADVERSE REACTIONS

Associated with Discontinuation of Treatment

Approximately 16% of the 453 patients who received mirtazapine tablets in U.S. 6-week controlled clinical trials discontinued treatment due to an adverse experience, compared to 7% of the 361 placebo-treated patients in those studies. The most common events (≥ 1%) associated with discontinuation and considered to be drug related (i.e., those events associated with dropout at a rate at least twice that of placebo) are included in Table 2.

Table 2: Common Adverse Events Associated with Discontinuation of Treatment in 6-Week US Mirtazapine Trials

Adverse Event	Percentage of Patients Discontinuing with Adverse Event	
	Mirtazapine (n=453)	Placebo (n=361)
Somnolence	10.4%	2.2%
Nausea	1.5%	0%

Commonly Observed Adverse Events in US Controlled Clinical Trials

The most commonly observed adverse events associated with the use of mirtazapine tablets (incidence of 5% or greater) and not observed at an equivalent incidence among placebo-treated patients (mirtazapine incidence at least twice that for placebo) are listed in Table 3.

Table 3: Common Treatment-Emergent Adverse Events Associated with the Use of Mirtazapine in 6-Week US Trials

Adverse Event	Percentage of Patients Reporting Adverse Event	
	Mirtazapine (n=453)	Placebo (n=361)
Somnolence	54%	18%
Increased Appetite	17%	2%
Weight Gain	12%	2%
Dizziness	7%	3%

Table 4: Incidence of Adverse Clinical Experiences*(≥1%) in Short-Term US Controlled Studies

Body System Adverse Clinical Experience	Mirtazapine (n=453)	Placebo (n=361)
Body as a Whole		
Asthenia	8%	5%
Flu Syndrome	5%	3%
Back Pain	2%	1%
Digestive System		
Dry Mouth	25%	15%
Increased Appetite	17%	2%
Constipation	13%	7%
Metabolic and Nutritional Disorders		
Weight Gain	12%	2%
Peripheral Edema	2%	1%
Edema	1%	0%
Musculoskeletal System		
Myalgia	2%	1%
Nervous System		
Somnolence	54%	18%
Dizziness	7%	3%
Abnormal Dreams	4%	1%
Thinking Abnormal	3%	1%
Tremor	2%	1%
Confusion	2%	0%
Respiratory System		
Dyspnea	1%	0%
Urogenital System		
Urinary Frequency	2%	1%

* Events reported by at least 1% of patients treated with mirtazapine are included, except the following events which had an incidence on placebo greater than or equal to mirtazapine: headache, infection, pain, chest pain, palpitation, tachycardia, postural hypotension, nausea, dyspepsia, diarrhea, flatulence, insomnia, nervousness, libido decreased, hypertonia, pharyngitis, rhinitis, sweating, amblyopia, tinnitus, taste perversion.

ECG Changes

The electrocardiograms for 338 patients who received mirtazapine tablets and 261 patients who received placebo in 6-week, placebo-controlled trials were analyzed. 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.

Other Adverse Events Observed During the Premarketing Evaluation of Mirtazapine

During its premarketing assessment, multiple doses of mirtazapine tablets were administered to 2796 patients in clinical studies. The conditions and duration of exposure to mirtazapine varied greatly, and included (in overlapping categories) open and double-blind studies, uncontrolled and controlled studies, inpatient and outpatient studies, fixed-dose and titration studies. Untoward events associated with this exposure were recorded by clinical investigators using terminology of their own choosing. 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 event categories.

In the tabulations that follow, reported adverse events were classified using a standard COSTART-based dictionary terminology. The frequencies presented, therefore, represent the proportion of the 2796 patients exposed to multiple doses of mirtazapine who experienced an event of the type cited on at least 1 occasion while receiving mirtazapine. All reported events are included except those already listed in Table 4, those adverse experiences subsumed under COSTART terms that are either overly general or excessively specific so as to be uninformative, and those events for which a drug cause was very remote. It is important to emphasize that, although the events reported occurred during treatment with mirtazapine, they were not necessarily caused by it.

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 1 or more occasions in at least 1/100 patients; infrequent adverse events are those occurring in 1/100 to 1/1000 patients; rare events are those occurring in fewer than 1/1000 patients. Only those events not already listed in Table 4 appear in this listing. Events of major clinical importance are also described in the WARNINGS and PRECAUTIONS sections.

Body as a Whole:

frequent: malaise, abdominal pain, abdominal syndrome acute; *infrequent:* chills, fever, face edema, ulcer, photosensitivity reaction, neck rigidity, neck pain, abdomen enlarged; *rare:* cellulitis, chest pain substernal.

Cardiovascular System:

frequent: hypertension, vasodilatation; *infrequent:* angina pectoris, myocardial infarction, bradycardia, ventricular extrasystoles, syncope, migraine, hypotension; *rare:* atrial arrhythmia, bigeminy, vascular headache, pulmonary embolus, cerebral ischemia, cardiomegaly, phlebitis, left heart failure.

Digestive System:

frequent: vomiting, anorexia; *infrequent:* eructation, glossitis, cholecystitis, nausea and vomiting, gum hemorrhage, stomatitis, colitis, liver function tests abnormal; *rare:* tongue discoloration, ulcerative stomatitis, salivary gland enlargement, increased salivation, intestinal obstruction, pancreatitis, aphthous stomatitis, cirrhosis of liver, gastritis, gastroenteritis, oral moniliasis, tongue edema.

Endocrine System:

rare: goiter, hypothyroidism.

Hemic and Lymphatic System:

rare: lymphadenopathy, leukopenia, petechia, anemia, thrombocytopenia, lymphocytosis, pancytopenia.

Metabolic and Nutritional Disorders:

frequent: thirst; *infrequent:* dehydration, weight loss; *rare:* gout, SGOT increased, healing abnormal, acid phosphatase increased, SGPT increased, diabetes mellitus, hyponatremia.

Musculoskeletal System:

frequent: myasthenia, arthralgia; *infrequent:* arthritis, tenosynovitis; *rare:* pathologic fracture, osteoporosis fracture, bone pain, myositis, tendon rupture, arthrosis, bursitis.

Nervous System:

frequent: hypesthesia, apathy, depression, hypokinesia, vertigo, twitching, agitation, anxiety, amnesia, hyperkinesia, paresthesia; *infrequent:* ataxia, delirium, delusions, depersonalization, dyskinesia, extrapyramidal syndrome, libido increased, coordination abnormal, dysarthria, hallucinations, manic reaction, neurosis, dystonia, hostility, reflexes increased, emotional lability, euphoria, paranoid

reaction; *rare:* aphasia, nystagmus, akathisia (psychomotor restlessness), stupor, dementia, diplopia, drug dependence, paralysis, grand mal convulsion, hypotonia, myoclonus, psychotic depression, withdrawal syndrome, serotonin syndrome.

Respiratory System:

frequent: cough increased, sinusitis; *infrequent:* epistaxis, bronchitis, asthma, pneumonia; *rare:* asphyxia, laryngitis, pneumothorax, hiccup.

Skin and Appendages:

frequent: pruritus, rash; *infrequent:* acne, exfoliative dermatitis, dry skin, herpes simplex, alopecia; *rare:* urticaria, herpes zoster, skin hypertrophy, seborrhea, skin ulcer.

Special Senses:

infrequent: eye pain, abnormality of accommodation, conjunctivitis, deafness, keratoconjunctivitis, lacrimation disorder, 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.

Other Adverse Events Observed During Postmarketing Evaluation of Mirtazapine

Adverse events reported since market introduction, which were temporally (but not necessarily causally) related to mirtazapine therapy, include 4 cases of the ventricular arrhythmia torsades de pointes. In 3 of the 4 cases, however, concomitant drugs were implicated. All patients recovered.

Cases of severe skin reactions, including Stevens-Johnson Syndrome, bullous dermatitis, erythema multiforme and toxic epidermal necrolysis have also been reported.

DRUG ABUSE AND DEPENDENCE

Controlled Substance Class

Mirtazapine orally disintegrating tablets are not a controlled substance.

Physical and Psychologic Dependence

Mirtazapine orally disintegrating tablets have 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 behavior, 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 mirtazapine orally disintegrating tablet misuse or abuse (e.g., development of tolerance, incrementations of dose, drug-seeking behavior).

OVERDOSAGE

Human Experience

There is very limited experience with mirtazapine orally disintegrating tablets overdose. In

premarketing clinical studies, there were 8 reports of mirtazapine overdose alone or in combination with other pharmacological agents. The only drug overdose death reported while taking mirtazapine was in combination with amitriptyline and chlorprothixene in a non-US clinical study. Based on plasma levels, the mirtazapine dose taken was 30 to 45 mg, while plasma levels of amitriptyline and chlorprothixene were found to be at toxic levels. All other premarketing overdose cases resulted in full recovery. Signs and symptoms reported in association with overdose included disorientation, drowsiness, impaired memory, and tachycardia. There were no reports of ECG abnormalities, coma, or convulsions following overdose with mirtazapine alone.

Overdose Management

Treatment should consist of those general measures employed in the management of overdose with any drug effective in the treatment of major depressive disorder. Ensure an adequate airway, oxygenation, and ventilation. Monitor cardiac rhythm and vital signs. General supportive and symptomatic measures are also recommended. Induction of emesis is not recommended. Gastric lavage with a large-bore orogastric tube with appropriate airway protection, if needed, may be indicated if performed soon after ingestion, or in symptomatic patients. Because of the rapid disintegration of mirtazapine orally disintegrating tablets, pill fragments may not appear in gastric contents obtained with lavage. Activated charcoal should be administered. 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 center for additional information on the treatment of any overdose. Telephone numbers for certified poison control centers are listed in the *Physicians' Desk Reference* (PDR).

DOSAGE AND ADMINISTRATION

Initial Treatment

The recommended starting dose for mirtazapine orally disintegrating tablets is 15 mg/day, administered in a single dose, preferably in the evening prior to sleep. In the controlled clinical trials establishing the efficacy of mirtazapine in the treatment of major depressive disorder, the effective dose range was generally 15 to 45 mg/day. While the relationship between dose and satisfactory response in the treatment of major depressive disorder for mirtazapine has not been adequately explored, patients not responding to the initial 15-mg dose may benefit from dose increases up to a maximum of 45 mg/day. Mirtazapine has an elimination half-life of approximately 20 to 40 hours; therefore, dose changes should not be made at intervals of less than 1 to 2 weeks in order to allow sufficient time for evaluation of the therapeutic response to a given dose.

Administration of Mirtazapine Orally Disintegrating Tablets

Patients should be instructed to open tablet blister pack with dry hands and place the tablet on the tongue. The tablet should be used immediately after removal from its blister; once removed, it cannot be stored. Mirtazapine orally disintegrating tablets 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 tablet.

Elderly and Patients with Renal or Hepatic Impairment

The clearance of mirtazapine is reduced in elderly patients and in patients with moderate to severe renal or hepatic impairment. Consequently, the prescriber should be aware that plasma mirtazapine levels may be increased in these patient groups, compared to levels observed in younger adults without renal or hepatic impairment (see PRECAUTIONS and CLINICAL PHARMACOLOGY).

Maintenance/Extended Treatment

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

Switching Patients To or From a Monoamine Oxidase Inhibitor

Concomitant use of mirtazapine orally disintegrating tablets with MAOIs is contraindicated. At least 14 days should elapse between discontinuation of an MAOI and initiation of therapy with mirtazapine orally disintegrating tablets. In addition, at least 14 days should be allowed after stopping mirtazapine orally disintegrating tablets before starting an MAOI.

Discontinuation of Mirtazapine Treatment

Symptoms associated with the discontinuation or dose reduction of mirtazapine orally disintegrating tablets have been reported. Patients should be monitored for these and other symptoms when discontinuing treatment or during dosage reduction. A gradual reduction in the dose 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 PRECAUTIONS and ADVERSE REACTIONS).

HOW SUPPLIED

Mirtazapine Orally Disintegrating Tablets USP are available as:

15 mg: White to off-white, round, flat-faced, beveled-edge, unscored tablet. Debossed with stylized b over 241 on one side and plain on the other side.

Blister package of 30 tablets NDC 0591-2230-15

30 mg: White to off-white, round, flat-faced, beveled-edge, unscored tablet. Debossed with stylized b over 242 on one side and plain on the other side.

Blister package of 30 tablets NDC 0591-2231-15

Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature]. Protect from light and moisture. Use immediately upon opening individual tablet blister.

Rx only

Manufactured by:
TEVA PHARMACEUTICALS USA
Sellersville, PA 18960

Distributed by:
Watson Pharma, Inc.
Parsippany, NJ 07054 USA

Revised: August 2012

Medication Guide

Mirtazapine Orally Disintegrating Tablets USP

Read the Medication Guide that comes with mirtazapine orally disintegrating tablets before you start taking it and each time you get a refill. There may be new information. This Medication Guide does not

take the place of talking to your healthcare provider about your medical condition or treatment. If you have any questions about mirtazapine orally disintegrating tablets, talk to your healthcare provider.

What is the most important information I should know about mirtazapine orally disintegrating tablets?

Mirtazapine orally disintegrating tablets and other antidepressant medicines may cause serious side effects, including:

1. Suicidal thoughts or actions:

- **Mirtazapine orally disintegrating tablets and other antidepressant medicines may increase suicidal thoughts or actions** in some children, teenagers, or young adults within the **first few months of treatment or when the dose is changed.**
- Depression or other serious mental illnesses are the most important causes of suicidal thoughts or actions.
- Watch for these changes and call your healthcare provider right away if you notice:
  - New or sudden changes in mood, behavior, actions, thoughts, or feelings, especially if severe.
  - Pay particular attention to such changes when mirtazapine orally disintegrating tablets is started or when the dose is changed.

  Keep all follow-up visits with your healthcare provider and call between visits if you are worried about symptoms.

Call your healthcare provider right away if you have any of the following symptoms, or call 911 if an emergency, especially if they are new, worse, or worry you:

- attempts to commit suicide
- acting on dangerous impulses
- acting aggressive or violent
- thoughts about suicide or dying
- new or worse depression
- new or worse anxiety or panic attacks
- feeling agitated, restless, angry or irritable
- trouble sleeping
- an increase in activity or talking more than what is normal for you
- other unusual changes in behavior or mood
- feeling agitated, restless, angry or irritable
- trouble sleeping
- an increase in activity or talking more than what is normal for you
- other unusual changes in behavior or mood

Call your healthcare provider right away if you have any of the following symptoms, or call 911 if an emergency. Mirtazapine orally disintegrating tablets may be associated with these serious side effects:

2. Manic episodes:

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

3. Decreased White Blood Cells called neutrophils, which are needed to fight infections. Tell your

doctor if you have any indication of infection such as fever, chills, sore throat, or mouth or nose sores, especially symptoms which are flu-like.

4. Serotonin Syndrome or Neuroleptic Malignant Syndrome-like reactions. This condition can be life-threatening and may include:

- agitation, hallucinations, coma or other changes in mental status
- coordination problems or muscle twitching (overactive reflexes)
- racing heartbeat, high or low blood pressure
- sweating or fever
- nausea, vomiting, or diarrhea
- muscle rigidity

5. Seizures

6. Low salt (sodium) levels in the blood.
Elderly people may be at greater risk for this. Symptoms may include:

- headache
- weakness or feeling unsteady
- confusion, problems concentrating or thinking or memory problems

7. Sleepiness. It is best to take mirtazapine orally disintegrating tablets close to bedtime.

8. Severe skin reactions: Call your doctor right away if you have any or all of the following symptoms:

- severe rash with skin swelling (including on the palms of the hands and soles of the feet)
- painful reddening of the skin and/or blisters/ulcers on the body or in the mouth

9. Severe allergic reactions: trouble breathing, swelling of the face, tongue, eyes or mouth

- rash, itchy welts (hives) or blisters, alone or with fever or joint pain

10. Increases in appetite or weight. Children and adolescents should have height and weight monitored during treatment.

11. Increased cholesterol and triglyceride levels in your blood

Do not stop mirtazapine orally disintegrating tablets without first talking to your healthcare provider. Stopping mirtazapine orally disintegrating tablets too quickly may cause potentially serious symptoms including:

- dizziness
- abnormal dreams
- agitation
- anxiety
- fatigue
- confusion
- headache
- shaking
- tingling sensation
- nausea, vomiting
- sweating

What are mirtazapine orally disintegrating tablets?
Mirtazapine orally disintegrating tablets is a prescription medicine used to treat depression. It is important to talk with your healthcare provider about the risks of treating depression and also the risks of not treating it. You should discuss all treatment choices with your healthcare provider.

Talk to your healthcare provider if you do not think that your condition is getting better with mirtazapine orally disintegrating tablets treatment.

Who should not take mirtazapine orally disintegrating tablets?
Do not take mirtazapine orally disintegrating tablets if you:

- are allergic to mirtazapine or any of the ingredients in mirtazapine orally disintegrating tablets. See the end of this Medication Guide for a complete list of ingredients in mirtazapine orally disintegrating tablets.
- take a Monoamine Oxidase Inhibitor (MAOI). Ask your healthcare provider or pharmacist if you are not sure if you take an MAOI, including the antibiotic linezolid.
  - it is recommended that mirtazapine orally disintegrating tablets not be used in combination with an MAOI within 14 days of initiating or discontinuing therapy with an MAOI.

People who take mirtazapine orally disintegrating tablets close in time to an MAOI may have serious or even life-threatening side effects. Get medical help right away if you have any of these symptoms:

- high fever
- uncontrolled muscle spasms
- stiff muscles
- rapid changes in heart rate or blood pressure confusion
- loss of consciousness (pass out)

What should I tell my healthcare provider before taking mirtazapine orally disintegrating tablets?

Ask if you are not sure.

Before starting mirtazapine orally disintegrating tablets, tell your healthcare provider if you:

- Are taking certain drugs such as:
  - Triptans used to treat migraine headache
  - Medicines used to treat mood, anxiety, psychotic or thought disorders, including tricyclics, lithium, SSRIs, SNRIs, or antipsychotics
  - Tramadol used to treat pain
  - Over-the-counter supplements such as tryptophan or St. John's Wort
  - Phenytoin, carbamazepine, or rifampicin (these drugs can decrease your blood level of mirtazapine)
  - Cimetidine or ketoconazole (these drugs can increase your blood level of mirtazapine)
- Have or had:
  - liver problems
  - kidney problems
  - heart problems
  - seizures or convulsions
  - bipolar disorder or mania
  - a tendency to get dizzy or faint
- are pregnant or plan to become pregnant. It is not known if mirtazapine orally disintegrating tablets will harm your unborn baby. Talk to your healthcare provider about the benefits and risks of treating depression during pregnancy
- are breastfeeding or plan to breastfeed. Some mirtazapine may pass into your breast milk. Talk to your healthcare provider about the best way to feed your baby while taking mirtazapine orally disintegrating tablets

Tell your healthcare provider about all the
medicines that you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. Mirtazapine orally disintegrating tablets and some medicines may interact with each other, may not work as well, or may cause serious side effects.

Your healthcare provider or pharmacist can tell you if it is safe to take mirtazapine orally disintegrating tablets with your other medicines. Do not start or stop any medicine while taking mirtazapine orally disintegrating tablets without talking to your healthcare provider first.

If you take mirtazapine orally disintegrating tablets, you should not take any other medicines that contain mirtazapine including mirtazapine tablets.

How should I take mirtazapine orally disintegrating tablets?

- Take mirtazapine orally disintegrating tablets exactly as prescribed. Your healthcare provider may need to change the dose of mirtazapine orally disintegrating tablets until it is the right dose for you.
- Take mirtazapine orally disintegrating tablets at the same time each day, preferably in the evening at bedtime.
- Open the tablet blister pack with dry hands and place the tablet whole on the tongue, immediately after removal from the blister pack.
- Mirtazapine orally disintegrating tablets will disintegrate rapidly on the tongue and can be swallowed with saliva. No water is needed for taking it.
- Do not attempt to split the mirtazapine orally disintegrating tablets.
- It is common for antidepressant medicines such as mirtazapine orally disintegrating tablets to take up to a few weeks before you start to feel better. Do not stop taking mirtazapine orally disintegrating tablets if you do not feel results right away.
- Do not stop taking or change the dose of mirtazapine orally disintegrating tablets without first talking to your doctor, even if you feel better.
- Mirtazapine orally disintegrating tablets may be taken with or without food.
- If you miss a dose of mirtazapine orally disintegrating tablets, take the missed dose as soon as you remember. If it is almost time for the next dose, skip the missed dose and take your next dose at the regular time. Do not take two doses of mirtazapine orally disintegrating tablets at the same time.
  - If you take too much mirtazapine orally disintegrating tablets, call your healthcare provider or poison control center right away, or get emergency treatment.

What should I avoid while taking mirtazapine orally disintegrating tablets?

- Mirtazapine orally disintegrating tablets can cause sleepiness or may affect your ability to make decisions, think clearly, or react quickly. You should not drive, operate heavy machinery, or do other dangerous activities until you know how mirtazapine orally disintegrating tablets affect you.
- Avoid drinking alcohol or taking diazepam (a medicine used for anxiety, insomnia and seizures, for example) or similar medicines while taking mirtazapine orally disintegrating tablets. If you are uncertain about whether certain medication can be taken with mirtazapine orally disintegrating tablets, please discuss with your doctor.

What are the possible side effects of mirtazapine orally disintegrating tablets?

Mirtazapine orally disintegrating tablets may cause serious side effects, including all of those described in the section entitled “What is the most important information I should know about mirtazapine orally disintegrating tablets?"

Common possible side effects in people who take mirtazapine orally disintegrating tablets include:

- sleepiness
- increased appetite, weight gain
- dry mouth
- constipation
- dizziness
- abnormal dreams

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of mirtazapine orally disintegrating tablets. For more information, ask your healthcare provider or pharmacist.

CALL YOUR DOCTOR FOR MEDICAL ADVICE ABOUT SIDE EFFECTS. YOU MAY REPORT SIDE EFFECTS TO THE FDA AT 1-800-FDA-1088.

How should I store mirtazapine orally disintegrating tablets?

- Store mirtazapine orally disintegrating tablets at room temperature 68° to 77°F (20° to 25°C).
- Keep mirtazapine orally disintegrating tablets away from light and moisture.
- Use immediately upon opening individual tablet blister.

Keep mirtazapine orally disintegrating tablets and all medicines out of the reach of children.

General information about mirtazapine orally disintegrating tablets

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use mirtazapine orally disintegrating tablets for a condition for which it was not prescribed. Do not give mirtazapine orally disintegrating tablets to other people, even if they have the same condition. It may harm them.

This Medication Guide summarizes the most important information about mirtazapine orally disintegrating tablets. If you would like more information, talk with your healthcare provider. You may ask your healthcare provider or pharmacist for information about mirtazapine orally disintegrating tablets that is written for healthcare professionals.

For more information about mirtazapine orally disintegrating tablets call 1-800-272-5525 or go to www.watson.com.

What are the ingredients in mirtazapine orally disintegrating tablets?
Active ingredient: mirtazapine
Inactive ingredients 15 mg and 30 mg tablets: Aspartame, citric acid anhydrous, crospovidone, magnesium stearate, mannitol, microcrystalline cellulose, natural and artificial orange flavor, sodium bicarbonate, hypromellose, povidone, sugar spheres, Eudragit E100.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Manufactured by:
TEVA PHARMACEUTICALS USA
Sellersville, PA 18960

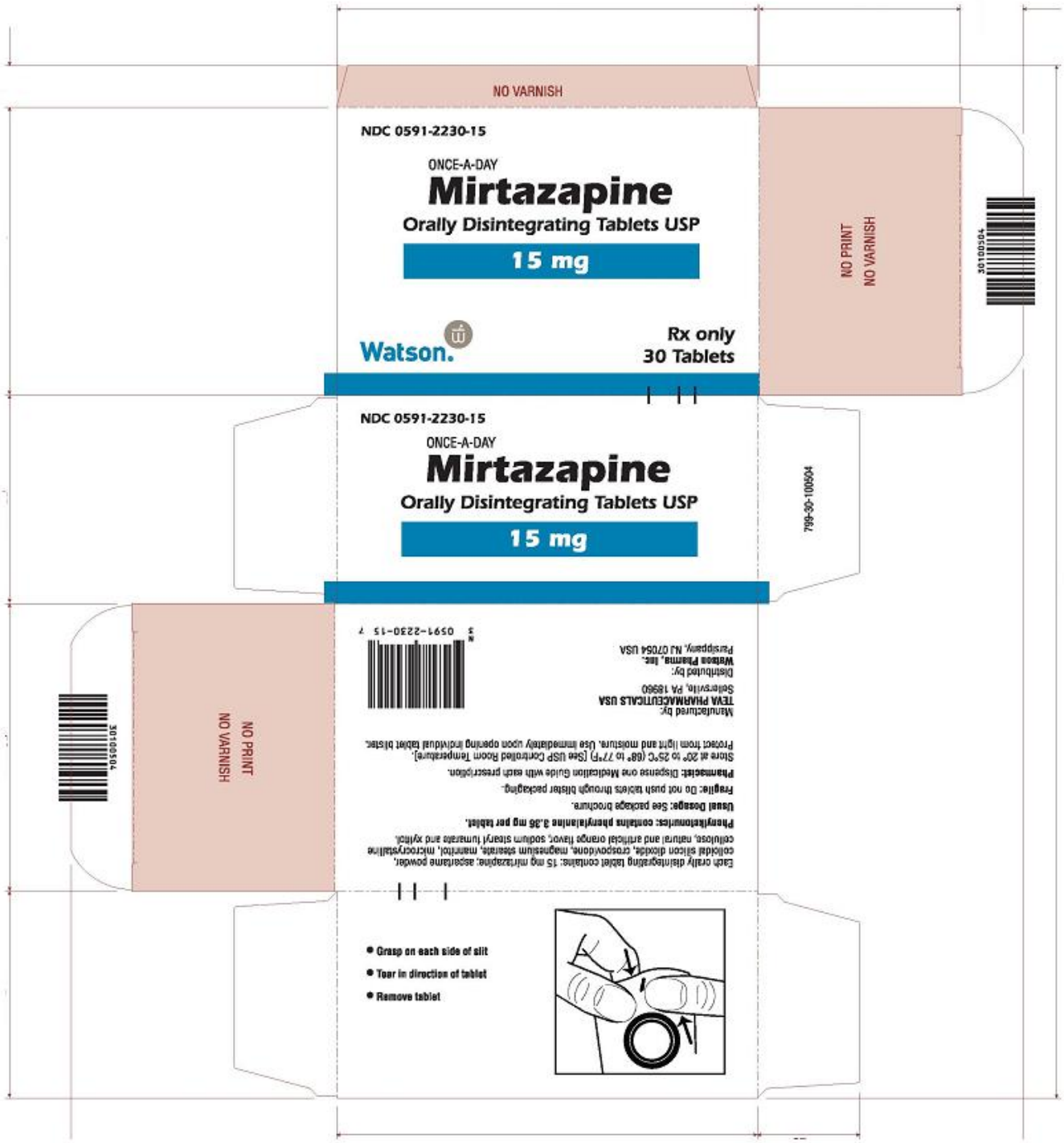
Distributed by:
Watson Pharma, Inc.
Parsippany, NJ 07054 USA

Revised: August 2012

Principal Display Panel - 15 mg

NDC 0591-2230-15
ONCE-A-DAY
Mirtazapine
Orally Disintegrating Tablets
15 mg

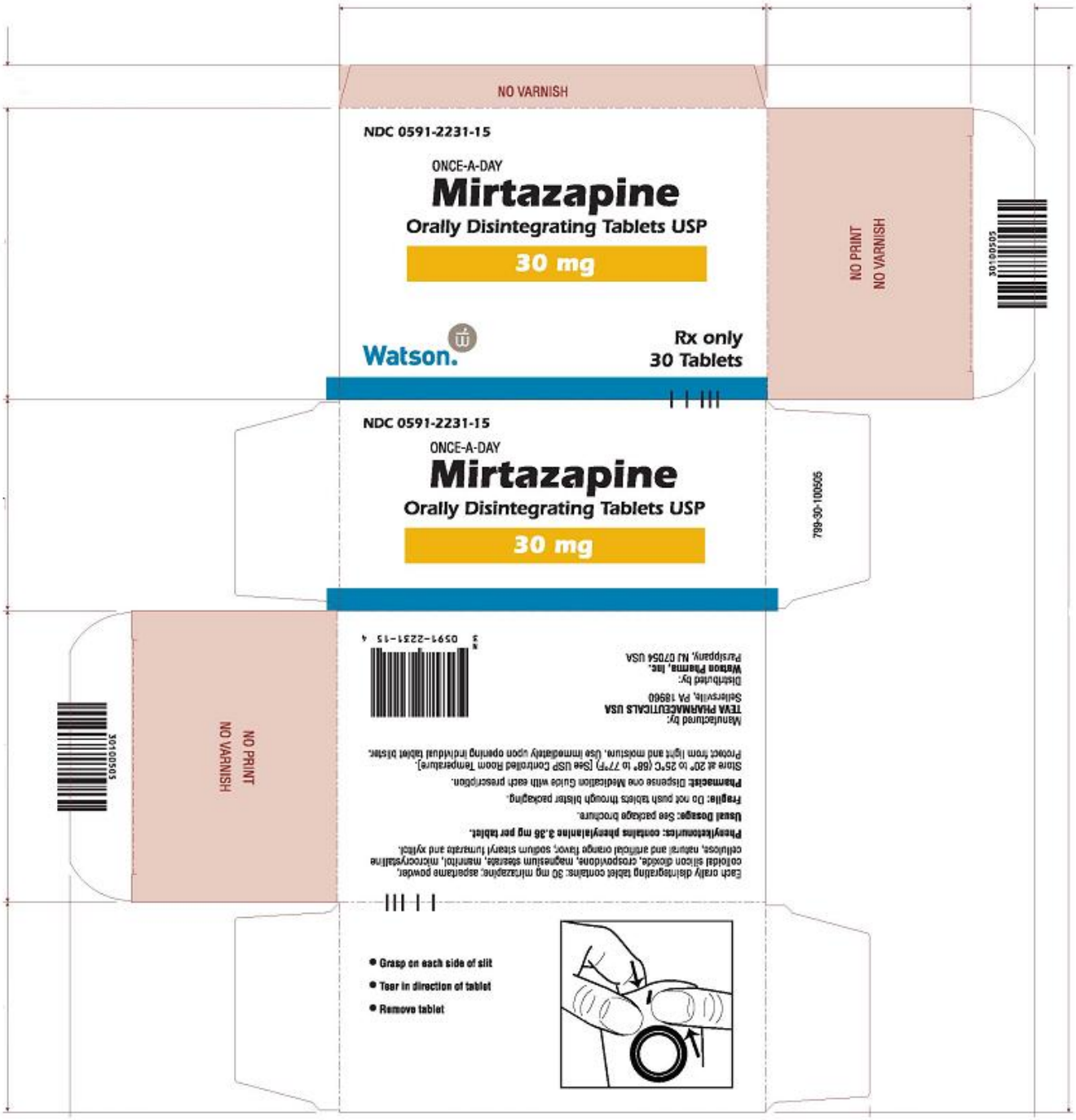
Watson®™ **Rx only**
30 Tablets



Principal Display Panel - 30 mg

NDC 0591-2231-15
ONCE-A-DAY
Mirtazapine
Orally Disintegrating Tablets
30 mg

Watson®™ **Rx only**
30 Tablets



MIRTAZAPINE

mirtazapine tablet, orally disintegrating

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG LABEL	**Item Code (Source)**	NDC:0591-2230

Route of Administration	ORAL	DEA Schedule	

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
MIRTAZAPINE (MIRTAZAPINE)	MIRTAZAPINE	15 mg

Inactive Ingredients

Ingredient Name	Strength
ASPARTAME	
SILICON DIOXIDE	
CROSPOVIDONE	
MAGNESIUM STEARATE	
MANNITOL	
CELLULOSE, MICROCRYSTALLINE	
.ALPHA.-TOCOPHEROL	
SODIUM STEARYL FUMARATE	
XYLITOL	
ETHYL BUTYRATE	
DIMETHYL BENZYL CARBINYL ACETATE	
ACETALDEHYDE	
ALCOHOL	
MALTODEXTRIN	
ORANGE OIL	
GRAPEFRUIT OIL	
CARYOPHYLLENE	
CITRUS SINENSIS FRUIT OIL	

Product Characteristics

Color	WHITE (white to off-white)	**Score**	no score
Shape	ROUND	**Size**	10mm
Flavor		**Imprint Code**	b;241
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0591-2230-15	5 in 1 CARTON		
1		6 in 1 BLISTER PACK		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA076307	12/01/2008	

MIRTAZAPINE

mirtazapine tablet, orally disintegrating

Product Information

Product Type	HUMAN PRESCRIPTION DRUG LABEL	**Item Code (Source)**	NDC:0591-2231
Route of Administration	ORAL	**DEA Schedule**	

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
MIRTAZAPINE (MIRTAZAPINE)	MIRTAZAPINE	30 mg

Inactive Ingredients

Ingredient Name	Strength
ASPARTAME	
SILICON DIOXIDE	
CROSPOVIDONE	
MAGNESIUM STEARATE	
MANNITOL	
CELLULOSE, MICROCRYSTALLINE	
.ALPHA.-TOCOPHEROL	
SODIUM STEARYL FUMARATE	
XYLITOL	
ETHYL BUTYRATE	
DIMETHYL BENZYL CARBINYL ACETATE	
ACETALDEHYDE	
ALCOHOL	
MALTODEXTRIN	
ORANGE OIL	
GRAPEFRUIT OIL	
CARYOPHYLLENE	
CITRUS SINENSIS FRUIT OIL	

Product Characteristics

Color	WHITE (white to off-white)	**Score**	no score
Shape	ROUND	**Size**	12mm
Flavor		**Imprint Code**	b;242
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0591-2231-15	5 in 1 CARTON		
1		6 in 1 BLISTER PACK		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA076307	12/01/2008	

Labeler - Watson Laboratories, Inc. (106931488)

Establishment

Name	Address	ID/FEI	Business Operations
AAIPharma Analytical Services		874223670	ANALYSIS(0591-2230, 0591-2230, 0591-2231)

Establishment

Name	Address	ID/FEI	Business Operations
AAIPharma Analytical Services		151838182	ANALYSIS(0591-2230, 0591-2230, 0591-2231)

Establishment

Name	Address	ID/FEI	Business Operations
Barr Laboratories Inc.		824749340	ANALYSIS(0591-2230, 0591-2231), MANUFACTURE(0591-2230, 0591-2231)

Establishment

Name	Address	ID/FEI	Business Operations
Barr Laboratories Inc.		002931751	ANALYSIS(0591-2230, 0591-2230, 0591-2231), LABEL(0591-2230, 0591-2230, 0591-2231), PACK(0591-2230, 0591-2230, 0591-2231)

Establishment

Name	Address	ID/FEI	Business Operations
Reed-Lane, Inc.		001819879	LABEL(0591-2230, 0591-2231), PACK(0591-2230, 0591-2231)

Establishment

Name	Address	ID/FEI	Business Operations
Teva Women's Health, Inc.		017038951	ANALYSIS(0591-2231), LABEL(0591-2230, 0591-2231), MANUFACTURE(0591-2231), PACK(0591-2230, 0591-2231)