xxxxxxxxx-5103

For the use of a Registered Medical Practitioner or a Hospital or a Laboratory

MENELAT

(Mirtazapine Tablets U.S.P., 30 mg / 45 mg)

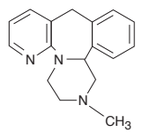
COMPOSITION

Each film coated tablet contains:

Mirtazapine U.S.P. …….. 30 mg / 45 mg

DESCRIPTION

Mirtazapine is an antidepressant for oral administration. It has a tetracyclic chemical structure unrelated to selective serotonin inhibitors, tricyclics or monoamine oxidase inhibitors (MAOI). Mirtazapine belongs to the piperanzinoazepine group of compounds. It is designated 1,2,3,4,10,14b-hexahydro-2-methylpyranzino [2,1-a] pyrido[2,3-c] benzazepine and has 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.

CLINICAL PHARMACOLOGY

Pharmacodynamics

The mechanism of action of mirtazapine as with 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_2 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 tablets are rapidly and completely absorbed following oral administration and have a half-life of about 20–40 hours. Peak plasma concentrations are reached within about 2 hours following an oral dose. The presence of food in the stomach has a minimal effect on both the rate and extent of absorption and does not require a dosage adjustment.

Mirtazapine is extensively metabolized after oral administration. Major pathways of biotransformation are demethylation and hydroxylation followed by glucuronide conjugation. In vitro data from human liver microsomes indicate that cytochrome 2D6 and 1A2 are involved in the formation of the 8-hydroxy 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 three times as high as that of the (+) enantiomer.

Plasma levels are linearly related to dose over a dose range of 15–80 mg. The mean elimination half-life of mirtazapine after oral administration ranges from approximately 20–40 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 - 10 μg/mL.

Special Populations

Geriatric

Elderly patients are more likely to have decreased renal function; care should be taken in dose selection. 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.

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 to elderly patients.

Pediatrics

Safety and effectiveness of mirtazapine in the pediatric population have not been established.

Gender

The mean elimination half-life of mirtazapine after oral administration ranges from approximately 20–40 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.

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 to patients with compromised renal function. (See Precautions).

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 to patients with compromised hepatic function. (See Precautions).

Nursing Mothers

It is not known whether mirtazapine is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when mirtazapine tablets are administered to nursing women.

INDICATIONS AND USAGE

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

The efficacy of mirtazapine in the treatment of major depressive disorder was established in six week controlled trials of outpatients whose diagnoses corresponded most closely to the Diagnostic and Statistical Manual of Mental Disorders – 3rd edition (DSM-III) category of major depressive disorder.

A major depressive episode (DSM-IV) implies a prominent and relatively persistent (nearly every day for at least 2 weeks) depressed or dysphoric mood that usually interferes with daily functioning, and includes at least five of the following nine 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 efficacy of mirtazapine in maintaining a response in patients with major depressive disorder for up to 40 weeks following 8-12 weeks of initial open-label treatment was demonstrated in a placebo-controlled trial. Nevertheless, the physician who elects to use mirtazapine for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient.

CONTRAINDICATIONS

Mirtazapine tablets are contraindicated in patients with a known hypersensitivity to mirtazapine or any of the exceipients.

WARNINGS

Clinical Worsening and Suicide Risk

All pediatric patients being treated with antidepressants for any indication should be 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. Such observation would generally include at least weekly face-to-face contact with patients or their family members or caregivers during the first 4 weeks of treatment, then every other week visits for the next 4 weeks, then at 12 weeks, and as clinically indicated beyond 12 weeks. Additional contact by telephone may be appropriate between face-to-face visits.

Adults with MDD or co-morbid depression in the setting of other psychiatric illness being treated with antidepressants should be observed similarly for clinical worsening and suicidality, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases.

Screening Patients for Bipolar Disorder:

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 tablets are not approved for use in treating bipolar depression.

Agranulocytosis

If a patient develops a sore throat, fever, stomatitis or other signs of infection, along with a low WBC count, treatment with mirtazapine 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 tablets, it is recommended that mirtazapine not be used in combination with an MAOI, or within 14 days of initiating or discontinuing therapy with an MAOI.

PRECAUTIONS

General

Somnolence

In the clinical study, 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 mirtazapine's potentially significant effects 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.

Dizziness

In the clinical 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 the clinical studies, appetite increase was reported in 17% of patients treated with mirtazapine, compared to 2% for placebo and 6% for amitriptyline. In the 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.

Cholesterol/Triglycerides

In the clinical 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% of patients exposed to mirtazapine in the clinical trials, compared to 0.3% of placebo patients and 2.0% 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 should be used with caution in patients with impaired hepatic function.

Activation of Mania/Hypomania

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

Care should be taken when mirtazapine is used in these patients.

Use in Patients with Concomitant Illness

Mirtazapine 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 to such patients.

Interference with Cognitive and Motor Performance

Mirtazapine may impair judgement, 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 therapy does not adversely affect their ability to engage in such activities.

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 to interact with other drugs.

Alcohol

Mirtazapine may increase the CNS depressant effect of alcohol. Patients should therefore be advised to avoid alcoholic beverages.

Pregnancy

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

Nursing

Patients should be advised to notify their physician if they are breast-feeding an infant.

Laboratory Tests

There are no routine laboratory tests recommended.

DRUG INTERACTIONS

Drugs Affecting Hepatic Metabolism

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

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

In *in vivo*-interaction studies, mirtazapine did not influence the pharmacokinetics of risperidone or paroxetine (CYP2D6 substrate), carbamazepine (CYP3A4 substrate), amitriptyline and cimetidine.

Mirtazapine dosed at 30 mg once daily caused a small but statistically significant increase in the INR in subjects treated with warfarin. As at a higher dose of mirtazapine a more pronounced effect cannot be excluded. It is advisable to control the prothrombin time in case of concomitant treatment of warfarin with mirtazapine.

Alcohol

The impairment of cognitive and motor skills produced by mirtazapine has been shown to be additive with those produced by alcohol. So, patients should be advised to avoid alcohol while taking mirtazapine.

Diazepam

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

ADVERSE REACTIONS

Associated with Discontinuation of Treatment

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) included:

Common Adverse Events Associated with Discontinuation of treatment in 6-week 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 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) were:

Common Treatment-Emergent Adverse Events Associated with the Use of mirtazapine in 6-week 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%

Adverse Events Occurring at an Incidence of 1% or More Among Mirtazapine Treated Patients

INCIDENCE OF ADVERSE CLINICAL EXPERIENCES (≥ 1%) IN SHORT-TERM US CONTROLLED STUDIES

Body System Adverse Clinical Experience	Mirtazapine	Placebo
Body as a whole		
Asthenia	8%	5%
Flu syndrome	5%	3%
Back Pain	2%	1%
Digestive System		
Dried Mouth	25%	15%
Increaesd 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%

ECG Changes

In 6 weeks placebo-controlled trials of mirtazapine, the 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 Postmarketing Evaluation of Mirtazapine

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

DRUG ABUSE AND DEPENDENCE

Controlled Substance Class

Mirtazapine tablets are not a controlled substance.

Physical and Psychologic Dependence

Mirtazapine 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 misuse or abuse (e.g., development of tolerance, incrementations of dose, drug seeking behavior).

OVERDOSAGE

Human Experience

There is very limited experience with mirtazapine tablets overdose. The only drug overdose death reported while taking mirtazapine was in combination with amitriptyline and chlorprothixene in a non clinical study. Based on plasma levels, the mirtazapine dose taken was 30-45 mg, while plasma levels of amitriptyline and chlorprothixene were found to be at toxic levels. 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.

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.

DOSAGE AND ADMINISTRATION

Initial Treatment

The initial dose is 15 or 30 mg, taken preferably in the evening. The maintenance dose is usually between 15 mg and 45 mg per day.

Mirtazapine has an elimination half-life of approximately 20-40 hours; therefore, dose changes should not be made at intervals of less than one to two weeks in order to allow sufficient time for evaluation of the therapeutic response to a given dose.

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).

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 8-12 weeks of initial treatment at a dose of 15-45 mg/day. 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

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

STORAGE

Store below 30°C, Protected from light & moisture.

EXPIRY DATE

Do not use later than the date of expiry.

PRESENTATION

Mirtazapine Tablets are available in blister pack of 10 tablets.

torrent PHARMA

Manufactured by :

TORRENT PHARMACEUTICALS LTD.

Indrad-382 721, Dist. Mehsana, INDIA.